

COMBINATION PROPHYLAXIS OF POSTOPERATIVE DEEP VEIN THROMBOSIS

AN EVALUATION OF THREE COMBINED REGIMENS

By
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Malmö 1983

Lund

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Printed in offset by
Lidbergs Blankett AB
274 00 Skurup, Sweden

ACKNOWLEDGEMENTS

To ALL who assisted me, cooperated, discussed and gave invaluable criticism of this work I wish to express my sincere gratitude.

Sincere appreciation is extended to Professor Sven-Erik Bergentz for encouragement and support.

To Professor Bengt Zederfeldt for stimulating criticism.

To my former chief Associate Professor Torgil Hallböök who stimulated my interest in research.

In particular appreciated is the friendship, guidance and constructive criticism given by my tutor Associate Professor David Bergqvist.

Birgitta, my wife, Henrik and Ninni, our children, supported me throughout the whole study.

This study has been supported by grants from the Medical Faculty, University of Lund, Sweden, The Swedish Medical Research Council (Grant nos. 00759 and 05447), The Hulda Almroth Foundation, The Greta and Johan Kock Foundation, The National Swedish Association for Cardiovascular Diseases, Skaraborg County Council Development Fund, Sandoz AB, Täby, Sweden, Pharmacia AB, Uppsala, Sweden, Beiersdorf AB, Kungsbacka, Sweden.

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This survey is based on the following publications:

- I. Central haemodynamic effects of dextran 70, dihydroergotamine and their combination. A study in dogs.
Bengt Lindblad & David Bergqvist. Acta Chir Scand, 149: 459-465, 1983.
- II. Tissue blood flow and blood flow distribution after administration of dextran 70, dihydroergotamine and their combination. A study in dogs using the radioactive microsphere technique.
Bengt Lindblad & David Bergqvist. Acta Chir Scand, 149: 467-472, 1983.
- III. Changes in peripheral haemodynamics induced by dextran 70, dihydroergotamine, and their combination. A study using ultrasonic, serial phlebography, plethysmography, and isotope clearance techniques.
Bengt Lindblad, David Bergqvist, Torgil Hallböök & Sven-Eric Lindell. Submitted.
- IV. The pharmacokinetics of subcutaneous dihydroergotamine with and without dextran 70 infusion.
Bengt Lindblad, Eva Abisch & David Bergqvist. Europ J Clin Pharmacol, 24: 813-818, 1983.
- V. The effect of dihydroergotamine on platelets, coagulation and fibrinolysis, studied in healthy humans and in dogs.
Bengt Lindblad, David Bergqvist & Ulla Hedner. Thromb Res, in press.

VI. Does dihydroergotamine potentiate the thromboprophylactic effect of dextran?. A controlled prospective study in general and hip surgery.

David Bergqvist, Bengt Lindblad, Karl-Gösta Ljungström, Nils Persson & Torgil Hallböök. Submitted.

VII. Prevention of postoperative thromboembolic complications. A prospective comparison between dextran 70, dihydroergotamine heparin and a sulphated polysaccharide.

David Bergqvist, Hans O. Efsing, Torgil Hallböök & Bengt Lindblad. Acta Chir Scand 146:559-568, 1980.

VIII. The thromboprophylactic effect of graded elastic compression stockings in combination with dextran 70.

David Bergqvist & Bengt Lindblad. Submitted.

These articles are referred to in the text by the Roman numerals given above.

INTRODUCTION

Deep vein thrombosis occurs in more than fifty per cent of patients undergoing hip surgery or suffering from hemiparesis, and in a third of general surgery patients over 50 years of age. Most of these thrombi occur in the calf veins. Though to a lesser extent than thrombi located more proximally, deep vein thrombosis in the calf veins can cause pulmonary embolism, which is the most common surgical complication with a possibly fatal outcome. Another possible development is venous insufficiency.

A number of studies, in which the ^{125}I -fibrinogen uptake test was used, have demonstrated the value of prophylactic therapy in safeguarding against postoperative thrombosis. Nonetheless, the frequency of thromboembolism remains unacceptably high, particularly among patients undergoing hip surgery. The prophylactic agents most commonly used in Scandinavia are dextran 70 and low-dose heparin. The multiplicity of factors involved in the pathogenesis of thrombosis argues the need of preventive regimens aimed at counteracting several factors simultaneously - that is to say, combined prophylactic treatment.

This study deals with the potential and the effects of three combinations of prophylactic methods: dihydroergotamine and dextran 70, dihydroergotamine and low-dose heparin, and graded compression stockings and dextran 70. Dihydroergotamine enhances tonus mainly in capacitance vessels, reduces blood pooling, and increases venous blood flow velocity. Venous circulation are also improved with graded compression stockings. Dextran reduces blood viscosity, inhibits the aggregation of blood corpuscular elements, interacts with factor VIII, and promotes the dissolution of thrombi. Heparin forms a complex with antithrombin III enhancing the inhibition of coagulation. Theroretically, therefore, these combinations should be beneficial in preventing postoperative thromboembolism. The main purpose of this study was to evaluate the thromboprophylactic effect of these combined regimens.

ON THE PATHOGENESIS OF THROMBOSIS

In 1856 Rudolf Virchow proposed three factors as being responsible for the development of venous thrombosis: changes in the vessel wall, changes in blood components, and changes in blood flow. By and large, this triad is still valid in any discussion of the pathogenesis of thrombosis.

VESSEL WALL ALTERATIONS

The vascular endothelium is an interface between the blood and underlying vascular structure consisting of a single cellular layer. Though little importance used to be attached to it in the pathogenesis of thrombosis, during the last decade several reports have shown the endothelial cell to be an active metabolic cell with several important properties. One is to maintain a thromboresistant surface.

Many substances are metabolized within the endothelial cell, several of which are of interest in the pathogenesis of thrombosis, for example: glucosaminoglycans, bradykinin, angiotensin, prostacyclin (PGI_2), leucotriens, plasminogen activators, factor VIII:R Ag (related antigen, von Willebrand factor), adenine nucleotides (Mason et al., 1977). Several may contribute to maintain thromboresistance (Majno & Joris, 1978) (Table I).

FACTORS OF POSSIBLE IMPORTANCE FOR THROMBO- RESISTANCE OF ENDOTHELIAL CELLS

HEPARAN SULPHATE

ADP- AMP-ASE

RECEPTORS FOR VASOACTIVE AMINES

PROSTACYCLIN, LEUCOTRIENS

PLASMINOGEN ACTIVATORS

Table I.

The thromboresistance has partly been ascribed to a heparin-like proteoglycan in the cell membrane, heparan sulphate (Thorgeirsson & Robertsson, 1978). Localized in the cell membrane are enzymes (ADP-ase, AMP-ase) capable of metabolizing proaggregatory ADP released from platelets or other sources to inactive adenine are present (Liebermann et al., 1977). The endothelial cell membrane also possesses receptors for vasoactive amines; these receptors are usually in a passive and proaggregatory state (Lollar & Owen, 1980).

Some of the substances metabolized within the endothelial cell are of particular interest in discussing the thromboresistance of the vessel wall: prostacyclin, plasminogen activators and factor VIII:R Ag. From arachidonic acid two unstable prostanoids are formed - prostacyclin (PGI_2) in the vessel wall, and thromboxane (TxA_2) within platelets (Fig. 1).

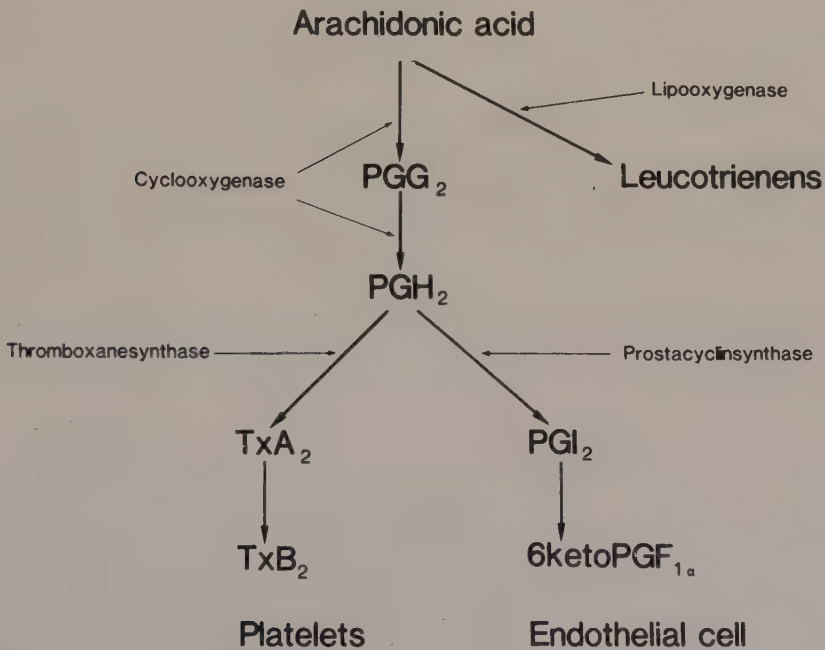


Fig. 1. Arachidonic acid metabolism.

Thromboxane A_2 causes vasoconstriction and has strong platelet aggregatory effects while prostacyclin causes vasodilation and is the strongest inhibitor of platelet aggregation known, though the part they play in the thrombogenesis is unclear. Leucotriens have also recently been found to interact with the platelet function. For reviews of prostanoids (prostaglandins and thromboxanes) see Samuelsson et al., 1980; Moncada, 1980; Hornstra, 1982).

Plasminogen activators (Todd & Nunn, 1967) may be released from endothelial cells by local stimuli, venous stasis, stress and some vasoactive substances (Nilsson & Pandolfi, 1970; Robertson et al., 1972; Cash, 1975; Mannucci et al., 1975; Nilsson et al., 1980). Plasminogen activator activity in the vein wall decreases after major surgery, and many patients developing postoperative deep vein thrombosis have an abnormally low plasminogen activator content in superficial hand veins (Ljungnér et al., 1983). There is no plasminogen activator activity within venous cusps where the development of thrombi often starts (Ljungnér & Bergqvist, in press).

Factor VIII:R Ag is of importance for the adhesion of platelets. The release of factor VIII:R Ag is related to plasminogen activator release from endothelial cells (Nilsson et al., 1982). The von Willebrand factor (Factor VIII:R Ag) has been localized within the endothelial cells (Bloom et al., 1973; Holmberg et al., 1974), but also within platelets (Howard et al., 1974). Postoperatively factor VIII: R Ag concentrations in plasma are increased (Nilsson, 1979), though this increase is of questionable importance in the pathogenesis of postoperative thrombosis.

Subendothelial connective tissue consists of collagens, proteoglycans, fibronectin and elastin among others. Collagen is important in stimulating platelet release and activating coagulation. Though endothelial injury causing exposure of the connective tissue is rare in venous thrombopathogenesis (Sevitt, 1974; Havig, 1977), in the endothelial lining there are gaps in which platelets, possibly activated, or granulocytes have a tendency

to adhere. These gaps are common in veins (Turitto & Baumgartner, 1982). Increased contractibility of the endothelial cell lining which opens and increases these gaps has been proposed as a causal factor in thrombus formation (Turitto & Baumgartner, 1982).

ALTERATIONS IN THE COMPONENTS OF BLOOD

Discussion of the changes in blood components has been divided in three parts: changes in platelets, in coagulation, and in the fibrinolytic system.

PLATELET ALTERATIONS

The subcellular structure of the disc-shaped platelet is shown schematically in Figure 2.

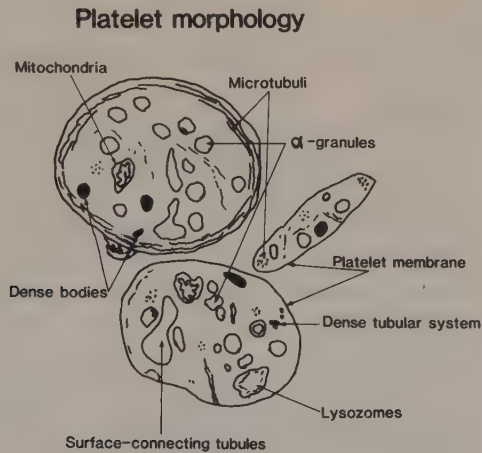


Fig. 2. Subcellular platelet structure.

Normally platelets do not adhere to the vascular endothelium. If the endothelium is damaged and subendothelial connective tissue exposed, platelet adhesion results. It is also possible that minor alterations, too small even to be visible in electron microscopy, modify local metabolism and result in platelet adhesion (Stewart et al., 1978 & 1980). Platelet adhesion also occurs if the properties of glycoproteins in the platelet membrane are changed thus enhancing platelet stickiness (Caen et al., 1976).

The von Willebrand factor (factor VIII:R Ag), produced and stored in the platelets, is probably necessary for platelet adhesion (Salzman, 1963). Erythrocytes and large plasmaproteins cause platelets to diffuse radially in the bloodstream, where they collide with the vessel wall; when this occurs at high shear rates, platelets can be deformed which is also important for platelet adhesion (Turitto & Weiss, 1980). These high shear rates do not occur in the venous circulation. Platelet adhesion is also triggered by thrombin (Czervionke et al., 1978).

When platelets adhere to the vessel wall or to other cells, the platelet release reaction is triggered, by which the contents of the dense bodies, α -granules and lysosomes, are liberated (Table II).

PLATELET RELEASE REACTION - GRANULES CONTENT RELEASED

<u>DENSE BODIES</u>	<u>α-GRANULES</u>	<u>LYSOSOMES</u>
ADP	ALBUMIN, FIBRINOGEN, FIBRONECTIN	β -GLUCURONIDASE
ATP	FACTOR V, FACTOR VIII: R Ag	β -GALACTOSIDASE
CALCIUM	PLATELET FACTOR 4, β -THROMBOGLOBULIN	BN-ACETYL GLUCOSAMIDASE
SEROTONIN	THROMBOSPONDIN	CYCLIC 3,5-NUCLEOTIDE
PYROPHOSPHATE	PLATELET DERIVED GROWTH FACTOR	PHOSPHODIESTERASE
POTASSIUM?	COLLAGENASE?, ELASTASE?	ENDOGLUCOSIDASE
	α_1 -ANTITRYPSIN?, α_2 -MACROGLOBULIN?	ARYL SULPHATASE
	C5-ACTIVATOR?, ANTIPLASMIN?	CATHEPSIN D, E
	ANTIUKINASE?, HMW-KININOGEN?	COLLAGENASE, ELASTASE
	BACTERICIDAL PROTEIN?	
	PERMEABILITY INCREASING PROTEIN?	

Table II. Substances released from platelets during release reaction (adapted from Niewiarowski, 1977 and other sources).

The release reaction may initiate platelet aggregation by anyone of at least three different pathways: by ADP, by thromboxane A_2 and by a lysolecithin - platelet activating factor (PAF). The effect of the two latter pathways may be mediated via ADP, or it may cause direct aggregation (Fig. 3). In several species the evidence for the existence of platelet activating factor is convincing, but it is less so in man (Cazenave et al., 1979; Hornstra, 1982).

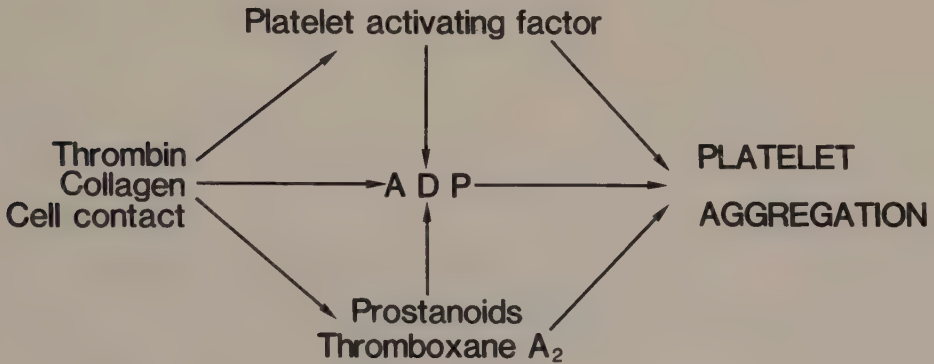


Fig. 3. The different pathways for platelet aggregation.

Of the substances released, serotonin induces local vasoconstriction and increases vascular permeability, platelet factor IV neutralizes heparin, and β -thromboglobulin inhibits prostacyclin production (De Gaetano, 1981). The platelet release reaction also renders fibrinogen binding sites on the platelet membrane receptive, which further enhances platelet adhesion (Hornstra, 1982).

ADP from other sources such as erythrocytes and damaged tissue has been considered to be of greater importance than ADP from the platelet release reaction, at least in the initiation of haemostatic plug formation (Born et al., 1976; Bergqvist et al., 1983). In this context the effects of serotonin-release seem to be of minor importance (Bergqvist & Arfors, 1976; Bergqvist et

al., 1983). Whether these observations also apply to venous thrombopathogenesis is not known.

After aggregation the platelet membrane is rearranged and a catalytic phospholipid surface, commonly known as platelet factor 3, is formed. It can interact at several junctures with both the intrinsic and extrinsic blood coagulation pathways (Semararo & Vermylen, 1977). Platelet factor 3 may thus induce discrete platelet dependent local activation of the coagulation system, the locally generated fibrin reinforcing thrombi already formed. Trauma results in an immediate decrease in platelet count, followed by an increase reaching a maximum between days 4 and 10 (Bergentz & Nilsson, 1961; Ygge, 1970), and platelet adhesiveness is increased (Negus et al., 1969). In spite of the importance of the platelets in initial haemostasis, there is no clear evidence that they initiate the development of venous thrombosis. Indeed, in an experimental model venous thrombi developed even when the platelet count was minimal (Olsson, 1974). Platelet behaviour is very dependent on shear rates; at low shear rates, as in the venous system, platelet activity is low but a larger amount of fibrin can be formed during such conditions since processing time is available. At high shear rates, as in the arterial system, platelet activity dominates (Turitto & Baumgartner, 1982).

ALTERATIONS IN BLOOD COAGULATION

The coagulation system may be divided into an intrinsic and an extrinsic system. The intrinsic system is activated by blood contact to negatively charged surfaces, followed by a cascade of reactions which activates factor X (Stuart factor) (Fig. 4). The extrinsic system is triggered by contact between plasma and injured cells (thromboplastin) suggesting a more local activation for the extrinsic pathway. Thrombin - a serine protease - is generated by both pathways, and converts fibrinogen to fibrin monomers which polymerize to fibrin. The polymerized fibrin is then stabilized by a transamidase - factor XIII (FSF).

It has recently been shown that thromboplastin release, resulting from disruption and denudation of the endothelium within the microcirculation may occur during surgical trauma (Stewart et al., 1981). Surgical trauma and endotoxins et cetera, also cause increased concentrations of tissue thromboplastin in monocytes (Giercksky et al., 1983). Factors such as these may result in the release of a large amount of tissue thromboplastin which in turn may activate the extrinsic clotting pathway in the veins where shear rates are low, giving time for the initial development of a venous thrombi to occur. Recently it was also shown that platelets do increase the thromboplastin synthesis in endothelial cells (Johnsen et al., 1983).

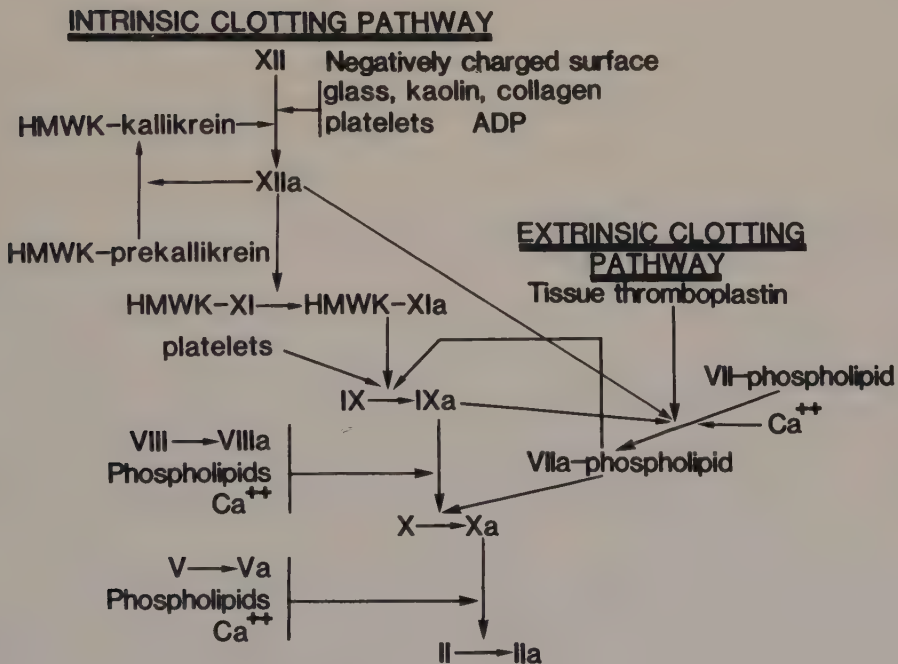


Fig. 4. The intrinsic and extrinsic clotting pathway.

The enzymatic coagulation cascade is modulated by inhibitors circulating in plasma, by inhibitors most probably adsorbed to the endothelial surface such as protein C, and by removal of activated clotting factors by the liver and the reticuloendothelial system. The most important inhibitor in plasma is antithrombin III, which inactivates not only thrombin but also other serine proteases such as kallikrein, plasmin and the activated forms of factors XII, XI, and X. Heparin greatly enhances the antiproteolytic properties of antithrombin III. The activation of thrombin activates protein C in the presence of membrane bound protein on the endothelial surface. Activated protein C degrades factor V and VIII. Thus the formation of thrombin results in local inhibition of further thrombin formation (Stenflo, 1976; Canfield et al., 1978; Owen, 1982; Suzuki et al., 1983).

Normally inactive coagulation factors circulate in the blood in excess. After trauma, concentrations or activity of factors II, V, VII, VIII and fibrinogen are increased (Ygge, 1970; Gallus et al., 1973), inhibitory effects are decreased and antithrombin III and protein C concentrations are reduced (Åberg et al., 1973; Griffin et al., 1982).

ALTERATIONS IN THE FIBRINOLYTIC SYSTEM

When plasminogen is activated plasmin is formed. Plasmin is a proteolytic enzyme with trypsin-like specificity which degrades fibrinogen and cross-linked fibrin into fragments called fibrin-fibrinogen degradation products. Plasmin also cleaves and activates factor XII (Hageman factor) and HMW-kininogen, and interacts with the complement system (Castellino & Violland, 1979).

Activators and inhibitors balance conversion of plasminogen to plasmin (Fig. 5).

The extrinsic fibrinolytic activators - urokinase-like activators and non-urokinase activators - are found in almost all tissue such as blood, endothelial cells, and uro-epithelium (Hedner

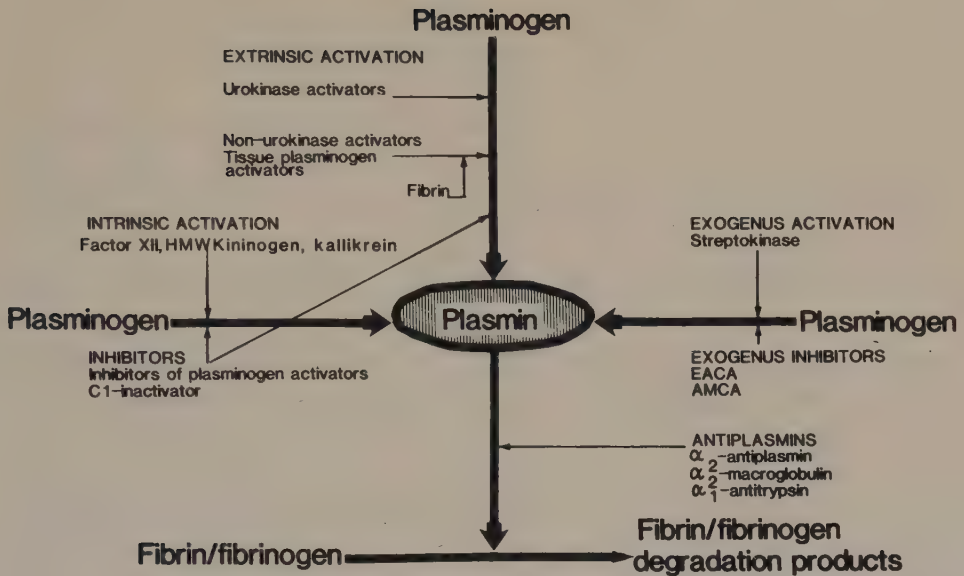


Fig. 5. The fibrinolytic system.

& Nilsson, 1981). The effects of the non-urokinase plasminogen activators in the vessel wall have been summarized above, as has the parallelism of plasminogen activator and factor VIII:R Ag release. Probably protein C not only interacts with the coagulation system (factor V, VIII) but, after activation on the endothelial cell membrane, also releases plasminogen activators from the endothelium (Comp & Esmon, 1981). If fibrin is present, locally increased fibrinolysis may occur, activating the potent proteolytic plasmin enzyme. Released tissue plasminogen activators are bound to the surface of fibrin where they activate the plasminogen turning it into the potent proteolytic enzyme plasmin which is thus localized to the site where its effect is needed (Wiman & Collen, 1978). Urokinase-like activators, which do not require the presence of fibrin for their activation, also degrade fibrinogen (Collen et al., 1983). Though probably of minor biological importance, an intrinsic fibrinolytic activation also exists, consisting of factor XII dependent activators (factor XII, HMW Kininogen and prekallikrein) (Hedner & Nilsson, 1981).

Plasminogen activator release is initiated by various stimuli such as stress, venous occlusion and vasoactive substances (Cash, 1975; Mannucci et al., 1975). Cathecolamine infusion increases the plasminogen activator activity but the process by which it does so seems to be independent of effects on the adrenergic receptors (Cash, 1975). It has been postulated that changes in vascular motility and tonus cause this increased release of plasminogen activators (Mannucci et al., 1975). However, many vasoactive substances do not affect the fibrinolytic function (Thomsen et al., 1964); conversely, certain substances without vasoactive properties may stimulate plasminogen activator release (Mannucci et al., 1975). Tissue plasminogen activators have recently been produced in cell cultures and by a DNA-hybrid technique (Pennica et al., 1983). There is a keen interest in using tissue plasminogen activators in thrombolytic therapy, as they are unlikely to cause the bleeding complications that occur with urokinase and streptokinase therapy (Collen et al., 1983).

Inhibitors of plasminogen activation and antiplasmins inhibit the fibrinolytic system. The inhibitors of plasminogen activation counteract with activated factor XII (Hedner & Martinsson, 1978) but, because of the difficulty of assessing these inhibitors (Hedner & Collen, 1976), they have been incompletely investigated. The antiplasmins consist mainly of α_2 -antiplasmin (Collen, 1976; Saldeen, 1976) and α_2 -macroglobulin (Laurell & Jeppson, 1975). α_2 -antiplasmin, which is available in great excess, is the primary inhibitor and rapidly forms a complex with plasmin, which is then removed from the circulation. Any excess plasmin, beyond the primary inhibitor's capacity to deal with, is then inactivated by the secondary inhibitor, α_2 -macroglobulin (Collen, 1976). α_1 -antitrypsin and antithrombin III are also antiplasmins.

Following trauma, fibrinolytic activity first increases (Bergentz & Nilsson, 1961; Leandroer, 1968), and then abates (Ygge, 1970; Gallus et al., 1973). This reduction seems to parallel the decrease of factor XII (Hedner et al., 1983). The importance of

alterations in the fibrinolytic system is indicated by the fact that many patients with major thromboembolic disease have defective fibrinolytic function (Isacson & Nilsson, 1972).

ALTERATIONS IN BLOOD FLOW

Venous stasis is an ill-defined term. When discussing changes in venous circulation volume flow, velocity, pulsatility and clearance from different venous segments should be defined.

Deep vein thrombi are mainly formed in the venous cusps, and in the calf muscle veins where blood flow is reduced by immobilization (McLachlin et al., 1960; Stamatakis et al., 1978).

The high incidence of thrombosis in paralyzed legs of hemiplegic patients illustrates that impaired venous flow is an important factor in the development of venous thrombosis (Cope et al., 1973; Gibbard et al., 1976; Warlow et al., 1976; Czechanowski &

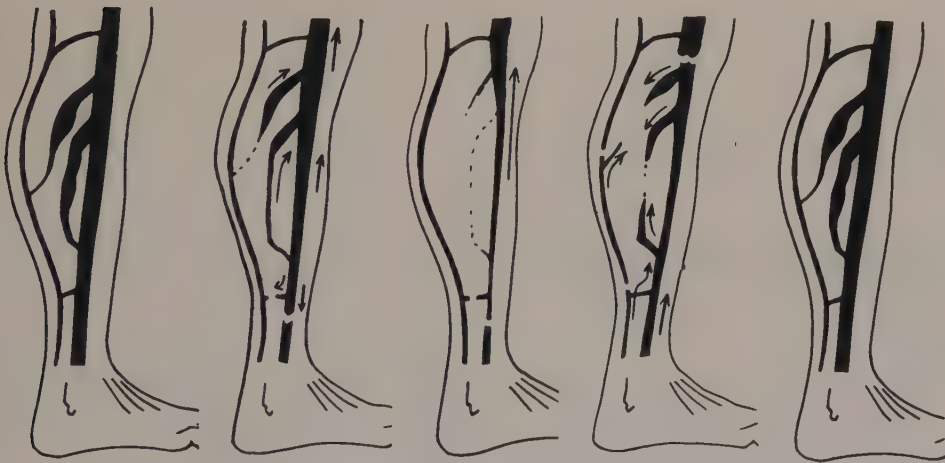


Fig. 6. The sequence of events during muscle contraction and relaxation with regard to the soleus arcade vein. Arrows indicate the direction of blood flow. a) Resting, b) early contraction, c) full contraction, d) relaxation, e) resting. (From Almén & Nylander, 1962 by courtesy of the authors).

Heinrich, 1981). Almén and Nylander (1962), using a phlebographic technique, showed that the calf muscle pump is essential for the venous circulation. They found that the soleus arcade vein, which lacks venous valve pockets, acts as a "suction pump" (Fig. 6). Using a combination of isotope clearance and contrast medium clearance, Nicolaides et al. (1972) showed that, with muscle relaxation and under general anaesthesia, the deep tibial veins of the legs cleared in approximately one minute, followed by slow clearance of the muscle veins which was complete in about ten minutes. In another study the clearance was somewhat slower (Lewis et al., 1976).

The velocity of venous blood flow has been the subject of many studies, in most of which various kinds of isotopes have been used to measure it (^{24}Na - Jönsson, 1951; Doran et al., 1964, ^{131}I -Hippuran - Meyerowitz & Nelson, 1964, ^{125}I -Hippuran - Kemble, 1971; Reickert, 1971, ^{133}Xe - Becker & Scampi, 1973; Mühe, 1974; Mühe et al., 1975). Though baseline velocity vary from situation to situation (1-10 cm/s), it seems reasonably certain that venous blood flow velocity is reduced during anaesthesia and in the postoperative period.

Using a Doppler technique, it has been confirmed that the venous blood flow velocity is decreased in the postoperative period (Kunz et al., 1981). In healthy volunteers prolonged bed rest also decreased venous blood flow velocity - approximately 50 % reduction after eight hours bed rest having been reported (Pauschinger et al., 1968).

Different anaesthetic techniques and different kinds of assisted ventilation during anaesthesia bring about changes in venous blood flow (Hodgson, 1964; Laaksonen et al., 1974; Modig et al., 1980). Retractor pressure during gall-bladder surgery and cooling of the legs also cause alterations (Lindström et al., 1977; Pflug et al., 1980).

During anaesthesia the pulsatility of venous blood flow is reduced (Lewis et al., 1972).

In anaesthetized patients volume blood flow has been examined in a few studies. With a thermodilution technique, a 50 % reduction in venous volume blood flow during anaesthesia has been found (Clark & Cotton, 1968). Using a plethysmographic technique, a 100% increase in arterial volume blood flow was noted, while reserve vein volume and venous emptying rate remained unchanged (Lindström et al., 1977). An increase in arterial volume blood flow is seen during epidural analgesia (Modig et al., 1980). Alterations in volume blood flow are of less importance than those in blood flow velocity in predisposing for thrombosis (Strandness & Sumner, 1975).

Rheologic changes are decisive factors in the pathogenesis of thrombi. Blood viscosity is increased following trauma (Gelin, 1956; Wessler, 1975), and increases with reduced blood flow (Dormandy & Edelman, 1973). Flow retardation causes tissue hypoxia and lactic acidosis, which stimulates vasodilation and further augments flow stagnation (Schmid-Schönbein, 1983). In venous cusps recirculation zones with severe hypoxia are seen (Karino, 1983).

HYPOTHESIS ON VENOUS THROMBUS FORMATION

A combination of several factors is necessary for the development of a venous thrombosis (Fig. 7).

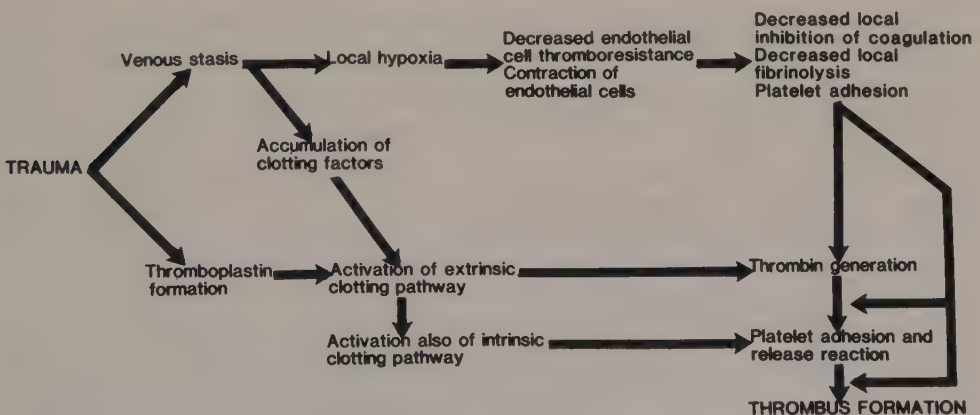


Fig. 7. Hypothesis of venous thrombus formation.

Many venous thrombi develop within the venous valve pockets and in the muscle veins of the calf where venous blood flow is retarded, viscosity increased and the blood hypoxic. This hypoxia, especially severe in recirculation zones, may induce metabolic changes in the endothelial cells, interacting with the thromboresistance. Increased contractility of the endothelial lining can be seen increasing the gaps between endothelial cells and exposing the subendothelium where platelets can adhere. Endothelial cell damage within the microcirculation may cause release of thromboplastin. In cases of severe tissue trauma there is a risk of circulating thromboplastin. Thus many factors may be involved and contribute in initiating the development of venous thrombosis. Venous stasis possibly promotes accumulation of clotting factors especially in the venous cusps. Activation of the extrinsic clotting pathway can cause local thrombin formation. Dysfunction of the regulating mechanisms prevents the enhancement of the fibrinolysis and protein C activation. Decreased thromboresistance, and local thrombin generation, may result in platelet adhesion to the endothelium. From the platelet release reaction, and perhaps from other sources, ADP is released causing platelet aggregation. Local activation of the clotting system (both pathways) and the absence of an activated fibrinolytic system, may enhance fibrin generation and thrombus formation and a manifest venous thrombosis may develop.

The multiplicity of factors involved in the pathogenesis of deep vein thrombosis justifies the assumption that optimal prophylaxis against deep vein thrombosis should interact with as many factors as possible. Since the efficacy of current prophylactic regimens is not optimal, combined prophylaxis appears to offer rewarding possibilities.

REVIEW OF PROPHYLACTIC METHODS

Since the introduction of the fibrinogen uptake test, several reports have shown a high incidence of postoperative thrombotic complications. The incidence increases mainly with age and varies between different types of operation. A clear difference is seen between those undergoing elective and emergency surgery, and between those having general and orthopaedic surgery (for review see Bergqvist, 1983).

The prophylactic methods may be divided into mechanical and pharmacological methods. Combined regimens have also been evaluated. In the following these methods will be discussed separately.

COMPRESSION METHODS

The prevention of "stasis" in the calf veins reduces the risk of development of deep venous thrombosis. It has been clearly shown that graded elastic compression stockings, electrical calf muscle stimulation, and intermittent calf compression with inflatable boots improve venous circulation (Nicolaidis et al., 1972; Becker & Schampi, 1973; Mühe, 1974; Sigel et al., 1975; Ah-See et al., 1976; Harris et al., 1976; Lewis et al., 1976). One exception in improved venous circulation may be intermittent calf compression. Contrast medium clearance time, evaluated phlebographically, is markedly reduced (Nicolaidis et al., 1972; Lindblad, unpublished data), but this could be due to "pendular" shifts in blood flow (Bergqvist et al., 1982). Sequential intermittent calf compression with inflatable boots seems to be a better alternative (Nicolaidis et al., 1980).

Recent studies of graded stockings have shown that clearance from calf veins is optimal when a graded compression with about 20 mm Hg pressure at the ankle and proximal reduction is applied (Siegel et al., 1975; Lewis et al., 1976; Partsch & Kahn, 1982). Such graded compression stockings are widely used, especially in the USA.

The effectiveness of graded stockings and other compression methods in preventing thromboembolism has been evaluated by several groups and has been shown to be satisfactory in general and urologic patients (Hull & Hirsch, 1981; Kakkar, 1981a; Bergqvist, 1983), but inadequate in patients undergoing hip surgery. Lately Hartman et al. (1982) and Hull et al. (1983a) have shown beneficial results in elective hip surgery with sequential intermittent calf compression. Compression methods do not interfere with haemostasis. The main drawback to the prolonged use of electrical calf muscle stimulation and of intermittent calf compression is patient discomfort, while graded compression stockings are easy to handle and are well tolerated by patients (Allan et al., 1983).

ORAL ANTICOAGULANTS

Oral anticoagulants interfere with K-vitamin dependent clotting factors (factors II, VII, IX & X and proteins C, S & Z). Since the classical study by Sevitt & Gallagher (1959) showing reduced frequency of pulmonary embolism in hip fracture patients given anticoagulants many studies have been presented. Most of these studies have been made on patients undergoing hip fracture surgery. Though the efficacy of oral anticoagulants is well established (Hull & Hirsch, 1981, Kakkar, 1981a; Bergqvist, 1983), one of their drawbacks is that therapy must be adjusted individually and correlated to the effect on clotting variables. Reports of bleeding complications are numerous, and there are controversies over dosage, administration intervals, and the duration of prophylaxis. Since in hip fracture patients, its efficacy is not superior to that of other treatment, the use of oral anticoagulants nowadays is not widespread in Scandinavia.

LOW-DOSE HEPARIN

Heparin was purified in 1916, and since Jorpes clarified the structure (1936) and later presented data on the efficacy of heparin in preventing thrombus formation (Crafoord & Jorpes, 1941), numerous studies have been presented. Heparin is produced

from porcine intestinal mucosa and is a sulphated polysaccharide with varying molecular weight (6 000-30 000). Heparin forms a complex with antithrombin III, enhancing its serine proteolytic effects. Low-dose administration of heparin was introduced by Sharnoff et al. (1962). Several studies on the effect of lowdose heparin have been presented and are summarized in Table III.

Table III

The effects of low-dose heparin in the prevention of postoperative thrombotic complications.

	No. of studies	No. of patients	DVT-frequency (%)	
			Control group	Low-dose heparin
General surgery	35	5873	32	10
Elective hip surgery	12	1002	53	23
Hip fracture surgery	9	541	55	32

(from Bergqvist, 1983)

Figures corresponding to those by Bergqvist (1983) are given in reviews by Kakkar (1978 and 1981a) and by Hull & Hirsch (1981). To sum up, there is a good reduction of deep vein thrombosis in general surgery. Though also effective to some extent in hip surgery patients, further reduction is to be desired. There has been debate as to whether the intervals between heparin doses should be 8 or 12 hours; apparently both intervals are comparable in preventive effect, though bleeding complications are more common with shorter intervals. Ultra low-doses of heparin has also been suggested (Negus et al., 1980). There is also controversy over which heparin salt should be used - calcium or sodium; bleeding complications are equally frequent, but there are indications that local injection pain is less with the sodium heparin salt (Arendrup & Toftgaard, 1979). The use of low-dose heparin as prophylaxis against postoperative thromboembolism is worldwide.

HEPARIN ANALOGUES and LOW MOLECULAR WEIGHT HEPARIN

Heparin-like sulphated polysaccharides have recently been developed. The effect of different fragments and fractions of heparin (low molecular weight heparin, molecular weight 4 000-8 000) are under evaluation. These substances interact with the activation of factor X, while other serine proteases are less affected. Theoretically at least this property should reduce the number of bleeding complications, and there is experimental evidence that this is true for low molecular weight heparin (molecular weight 4 000-5 000) (Esquivel et al., 1982).

A polysulphated galactosaminoglucan (SSHA) has been evaluated by Kakkar et al. (1978) and Törnngren et al. (1983). SSHA proved as effective as low-dose heparin in preventing deep venous thrombosis postoperatively, and no differences in bleeding variables were noted. Embolic complications were equally frequent in groups of patients receiving Ca^{++} -heparin, Na^+ heparin or SSHA (Kakkar, 1983a), though bleeding complications were frequent in the SSHA group. Two variants of sodium pentosan polysulphate - SP54 and PZ68 - have also been studied. SP54 has been found as effective as low-dose heparin (Joffe, 1976; Morin et al., 1978; Immelmann et al., 1981). The effect of PZ68 will be discussed on page 47.

The effectiveness of low molecular weight heparin is under evaluation. Experimental findings differ greatly between different heparin fragments and fractions, and variations in the processing technique also produce different effects. Preliminary data from an uncontrolled study by Kakkar's group are favourable (Kakkar, 1983b). The inhibitory effect of a heparin fragment (molecular weight 5 000) on factor X_a is greater, and the half life is longer, than that of conventional heparin (Bergqvist et al., in press). This may be of practical importance, since it lends support to the use of longer intervals between doses.

DRUGS AFFECTING PLATELET ACTIVATION

Among antiplatelet drugs, attention has mainly been focused on acetyl salicylic acid inhibiting the platelet release reaction and interfering with the catalysation achieved by cyclooxygenase whereby thromboxane A_2 and prostacyclin generation is affected. In acetyl salicylic acid therapy, the size of doses and the intervals between them are currently the subjects of debate. In studies on the effect of acetyl salicylic acid, quite different doses and intervals have been used. The effect of acetyl salicylic acid in preventing venous thromboembolic complications is open to question, but when combined with dipyridamole a reduced frequency of thrombosis in general surgery patients has been reported (Hull & Hirsch, 1981; Kakkar, 1981a; Bergqvist, 1983). Other antiplatelet drugs such as sulphinpyrazone, hydroxychloroquine, flurbiprofen and ticlopedine have shown little effect. New substances are under development with more specific interactions with platelet metabolism and other phases of platelet activation. The effects of these drugs are uncertain and they may interact at too late a stage in the platelet activation (Verstraete, 1982). One exception may be a nonapeptide, which binds to exposed collagen and decreases platelet adhesion (Legrand et al., 1980). One prerequisite for platelet inhibitors to function thromboprophylactically is an important role of platelets initially in the development of venous thrombosis.

DEXTRAN

Dextran is a polysaccharide formed by strains of *Leuconostoc mesenteroides*. Grönwall and Ingelmann (1944) showed that, because of its high hydrophilism, dextran was suitable as a plasma volume expander, and for this reason the use of dextran is widespread. During the 1950s several reports on haemostatic alterations due to dextran were presented, and in an experimental study it was found that dextran had an antithrombotic effect (Borgström et al., 1959). Koekenberg (1961) verified this antithrombotic effect in a clinical study. Several studies outlining this thromboembolic prophylactic effect have been presented and its

use is widespread, especially in Scandinavia.

Dextran 70 (medium molecular weight 70 000) has been used in most studies, but dextran 40 in some (medium molecular weight 40 000). In table IV the effect of dextran 70 is summarized.

Table IV

The effects of dextran 70 in the prevention of postoperative thrombotic complications.

	No of studies	No of patients	<u>DVT frequency (%)</u>	
			Control group	Dextran treated
General surgery	11	1701	27	20
Elective hip surgery	2	247	41	42
Hip fracture surgery	5	361	56	29

(from Bergqvist, 1983)

Table V

Comparative studies between low-dose heparin and dextran 70 regarding the frequency of postoperative thrombotic complications.

	No of studies	No of pat.	<u>DVT frequency (%)</u>		
			Control*	Low-dose heparin	Dextran 70 treatment
General surgery	4	894	32	9	23
Elective hip surgery	3	354	63	58	44
Hip fracture surgery	2	171	91	52	42

* Control group not included in all studies

(from Bergqvist, 1983)

The figures given in Table IV (Bergqvist, 1983) agree with those in other reviews (Bergentz, 1978; Kakkar, 1981a). The frequency of deep vein thrombosis is reduced only slightly in general surgery patients, but fatal pulmonary embolism is prevented as effectively as by low-dose heparin (Gruber et al., 1980). In hip surgery the effects of dextran 70 and low-dose heparin are comparable (Table V), though major thrombi (bilateral or femoral thrombi) are perhaps even more effectively reduced by dextran treatment.

DIHYDROERGOTAMINE

For centuries diseased rye has been known to cause poisoning characterized by gangrena, abortion and convulsions. The substances causing this, commonly called the ergot, are produced by a fungus (*Claviceps purpurea*). In addition to naturally occurring ergot alkaloids, hydrogenation led to the development of dihydroergotamine methansulphonate (Stoll & Hofmann 1943). Dihydroergotamine has α -receptor affinity but also binds to serotonergic and dopaminergic receptors. Dihydroergotamine was initially used in the treatment of migraine and other types of vascular headache. Beneficial results were later achieved in the treatment of hypotension (both orthostatic and induced by anaesthesia). Recently a preventive effect against postoperative thromboembolism has been observed. Used alone, its effect is insufficient (Lindblad, 1983), but when combined with low-dose heparin results are more satisfactory. The effects of this combination is discussed on page 29.

COMBINED PROPHYLACTIC REGIMENS

Few studies have been done on the effects of combined prophylactic regimens. The oral anticoagulation and dextran combination is potentially beneficial (van Geloven et al., 1977), especially in hip fracture patients (Korvald et al., 1973), but has been discarded because of attendant bleeding complications. The oral anticoagulation and low-dose heparin combination seems not to be additive (van Geloven et al., 1977). A low-dose heparin and dex-

tran 40 combination has not been found more effective than low-dose heparin by itself, but less effective than low-dose heparin combined with dihydroergotamine in patients undergoing elective hip surgery (Schöndorf & Weber, 1980), bleeding complications being comparable in all three groups. No additive effect results from combining low-dose heparin and dextran, and further evaluation of its effect on haemostasis is required before such a combination could be put into general use. Low-dose heparin combined with acetyl salicylic acid has been found beneficial in general surgery patients (Loew et al., 1977), but in hip surgery patients results have varied (Schöndorf & Hey, 1976; Flicoteaux et al., 1977; Yett et al., 1978). As already mentioned, acetyl salicylic acid combined with dipyridamole has been reported to be effective in general surgery patients.

COMBINED PROPHYLAXIS WITH COMPRESSION METHODS

Elastic bandaging in conjunction with antiplatelet therapy was found effective in one study (Tillberg, 1974). Törngren (1980) showed that low-dose heparin was more effective when used in combination with graded compression stockings.

Though intermittent calf muscle stimulation combined with dextran 70 was more effective than no treatment at all in reducing scintigraphically diagnosed pulmonary embolism (Browse et al., 1976), in another study this combination failed to reduce the frequency of deep vein thrombosis compared with dextran 70 treatment on its own (Smith et al., 1978). Roberts & Cotton (1975) showed that the frequency of deep vein thrombi was comparable between groups receiving intermittent calf compression alone or together with low-dose heparin. Beneficial results have recently been reported on the combination of low-dose heparin and sequential intermittent compression (Kakkar, personal communication), though the apparent additive effect here could have been due to sequential intermittent compression being more effective than conventional intermittent compression in enhancing venous circulation.

COMBINED PROPHYLAXIS WITH DIHYDROERGOTAMINE AND LOW-DOSE HEPARIN

Since Sagar et al. (1976) reported the beneficial and additive effects of combining dihydroergotamine and low-dose heparin, several similar studies have been presented. These are summarized in table VI.

Table VI

The effects of dihydroergotamine combined with low-dose heparin (5 000 IE) in the prevention of postoperative thrombotic complications.

	No of studies	No of patients	DVT frequency (%)	
			Low-dose* heparin	Dihydroergotamine+ low-dose heparin
General surgery	10	2655	18	9
Elective hip surgery	9	1156	40	22
Hip fracture surgery	2	170	21	18

* A group with low-dose heparin treatment was not included in all studies.

(from Lindblad, 1983).

In elective surgery patients the efficacy of low-dose heparin is enhanced by combination with dihydroergotamine, a finding also reported in an American multicentre study (Sasahara & DiSerio, 1983). In hip fracture patients, the effect of this combination is comparable to that of low-dose heparin alone, and no additive effect results (Lahnborg, 1980). Fatal pulmonary embolism is also reduced by the combination (Gruber, 1982). The beneficial results have led to studies on the prophylactic effect of combining a reduced heparin dose from 5 000 IE to 2 500 IE with dihydroergotamine treatment. This has been found as effective as

normal low-dose heparin prophylaxis in general surgery patients. In several studies this lower heparin dose reduce the number of bleeding complications but the gain in efficacy is probably insufficient to justify its use in high risk patients.

SUMMARY OF PROPHYLAXIS AGAINST THROMBOEMBOLISM

Low-dose heparin, especially when combined with dihydroergotamine, is efficacious in elective surgery, but in emergency surgery its effect is comparable to that of other prophylactic regimens. In general surgery, dextran treatment does not reduce the frequency of deep vein thrombosis as effectively as low-dose heparin. In hip surgery the effect of dextran 70 is at least comparable to that of low-dose heparin. Fatal pulmonary embolism is equally reduced by dextran 70 and low-dose heparin (International multicenter trial, 1975; Gruber et al., 1980). The combination of low-dose heparin and dihydroergotamine also effectively reduces fatal pulmonary embolism (Gruber, 1982). Methods of reducing venous "stasis" may be more effective when used in combination with other prophylactic measures, then when used on their own.

AIMS OF THIS INVESTIGATION

Studies on dihydroergotamine and dextran 70

To evaluate the effects of dextran 70 and dihydroergotamine, singly and in combination, on (I) central hemodynamics, (II) tissue blood flow and its distribution, and (III) peripheral haemodynamics.

To investigate the pharmacokinetics of subcutaneously administered dihydroergotamine, alone and in combination with dextran 70 (IV).

To evaluate the effect on platelets, coagulation and fibrinolysis of dihydroergotamine (V).

To evaluate the thromboprophylactic effect of dextran 70, alone and in combination with dihydroergotamine (VI).

Study on dihydroergotamine and low-dose heparin

To compare the preventive effect on postoperative thrombotic complications of low-dose heparin combined with dihydroergotamine, dextran 70, and a sulphated polysaccharide (PZ68) (VII).

Study on graded compression stockings and dextran 70

To ascertain whether graded compression stockings further reduce the frequency of postoperative thrombosis in patients receiving prophylaxis with dextran 70 (VIII).

MATERIAL and METHODS

Details in material, methods and statistics are given within each paper (I-VIII) and will only be summarized here.

PAPER I

The central haemodynamic effects were evaluated in 22 dogs. Nine dogs received dextran 70 followed by dihydroergotamine 15 minutes later, and another 9 dogs received dihydroergotamine 15 minutes before dextran 70. Of a further 4 dogs, 2 received dextran 70 only, and 2 dihydroergotamine only. All experiments lasted for 60 minutes, and half of them were prolonged to 240 minutes.

Comments

In studying central haemodynamics, two different methods of measuring cardiac output were used, thermodilution and radioactive microsphere technique, and results from both methods have been grouped together. In an investigation where these methods were compared, very high correlation was found, justifying the conflation of results (Arvidsson et al., in press).

The animal experiments were designed to elicit data on the effects of dihydroergotamine and dextran 70, used both singly and in combination. The number of animals in the groups receiving only dextran 70 or only dihydroergotamine was very small, but since the results parallel those of the other groups investigated the findings would appear to be valid.

PAPER II

Tissue blood flow and distribution of blood flow was investigated in 9 dogs using a radioactive microsphere technique.

Comments

The radioactive microsphere method, used to determine tissue

blood flow, contains several possible methodological and technical errors (Heymann et al., 1977). Attempts were made to ensure optimal dispersion of microspheres before injection. Though the injection was given rather slowly to avoid cardiac effects, the number of injected microspheres was approximately 3 million, thus providing optimal calculation premises. Despite the rather small series of experiments performed, results were uniform and any influence by technical errors seems minimal.

PAPER III

The peripheral haemodynamic effects of dihydroergotamine, dextran 70, and the two combined, were evaluated both experimentally and clinically. Data on peripheral haemodynamics were obtained by a variety of techniques: plethysmography, isotope clearance, contrast clearance during phlebography was made in patients during or after surgery, doppler measurement of arterial and venous blood flow velocity, ultrasonic determination of vessel area, and measurement of resting arterial blood flow by plethysmography in healthy humans.

Comments

Venous circulation is complex and experimental findings are partly dependent on the experimental model used. No golden rules for evaluation exist. Such differences in conditions as complete muscle relaxation under anaesthesia, partial muscle relaxation during immobilization, and active muscle contraction from exertion, will give rise to variations in venous circulation (Almén & Nylander, 1962; Hodgson, 1964; Lewis et al., 1976).

The limitations of methods for evaluating haemodynamics have been critically reviewed by Strandness & Sumner (1975). In this investigation a variety of techniques were used to meet different situations. Several different parameters were evaluated with more than one method, data from these were mainly in accordance suggesting that our conclusions are valid.

PAPER IV

Pharmacokinetic properties for dihydroergotamine, dextran 70, and their combination, were determined after single dose and multiple dose regimens.

Comments

The antrone method used for measuring dextran concentrations has good sensitivity in the range of concentrations under consideration in this study.

The radioimmunoassay used for determining dihydroergotamine concentrations had a detection limit close to the values found in the second phase of the dihydroergotamine concentration curve. Thus its sensitivity is not optimal for the determination of pharmacokinetic variables in the late β -phase. Another radioimmunoassay method for dihydroergotamine concentrations with an even lower detection limit only became available after this study was completed (Abisch, personal communication).

PAPER V

The effects of dihydroergotamine on platelets, coagulation and fibrinolysis were investigated ex vivo in healthy volunteers, fibrinolysis also investigated in dogs, and the effects of different concentrations of dihydroergotamine on platelet aggregation were evaluated in vitro.

Comments

The methods used in the haemostatic evaluation are in routine use at the department for Coagulation Disorders, Malmö General Hospital, and will not be discussed in detail here. When preparing platelet rich plasma, for example, heparin or citrate are added to collected blood. A possible effect on the platelets by the heparin or citrate added must be taken into consideration. Thus in vitro and ex vivo platelet investigations are not

optimal for evaluating platelet function.

PAPER VI

In a tricentric study, patients undergoing various kinds of surgery were investigated concerning the frequency of deep vein thrombosis. For prophylaxis dextran 70, alone or in combination with dihydroergotamine, was given. The groups investigated comprised elective general and urologic surgery, emergency general surgery, elective hip surgery and emergency hip surgery.

PAPER VII

In patients undergoing elective general and urologic surgery, comparison was made between dihydroergotamine combined with low-dose heparin and a sulphated polysaccharide (PZ68), and these two regimens were further compared with dextran 70 in elective and emergency hip surgery patients. Thrombotic complications were evaluated in all patients, and in elective hip surgery patients scintigraphically detected lung perfusion defects were also studied.

PAPER VIII

In elective general surgery patients, the effect of dextran 70 and graded compression stocking was evaluated with regard to postoperative thrombotic complications. The graded compression stockings were allocated by random order to either left or right leg, the other serving as a control.

In the prophylactic studies the development of thrombosis was screened with the ^{125}I -fibrinogen uptake test.

Comments

The ^{125}I -fibrinogen uptake test was used for detecting deep vein thrombosis. This method has been criticized because of its low sensitivity in the thigh region of the operated leg in hip

surgery patients, and the fact that isolated femoral thrombi may develop but remain undetected by the test (Harris et al., 1974). Stamatakis et al. (1977) have shown that compression of the femoral vein occurs during dislocation and rotation of the femur shaft in hip replacement operations. Whether this is due to a local compression from the femur shaft or to the rotation of the leg is unclear. Development of isolated femoral thrombi has been ascribed to this local effect on the vein. It has also been found that the approach used (i.e., lateral or posterior) will affect the frequency of isolated femoral thrombi, a lower frequency of such thrombi being reported when the posterior approach has been used (Gallus et al., 1983). Phlebographic studies have shown that isolated femoral thrombi are rather infrequent (Nillius & Nylander, 1979), and a negative ^{125}I -fibrinogen uptake test seems to minimize the possibility of femoral thrombi but, for maximal specificity, a positive test should be verified phlebographically (i.e., excluding wound haematoma).

Trial design, inclusion and exclusion criteria were determined before the investigations were commenced. The end-point in the clinical trials evaluating different prophylactic methods was deep vein thrombosis. End-points of greater clinical importance such as extension of thrombi, fatal pulmonary embolism and reduced death rate would have required a much larger number of patients for study. With the end-point used here, our conclusions remain valid but before recommendations as to the use of new prophylactic methods can be made, further investigations verifying our results are needed.

In one study (VII) perfusion scintigraphy was used in assessing the number of non-fatal pulmonary emboli. While a negative scan seems to exclude pulmonary embolism, a positive scan is not necessarily diagnostic evidence of pulmonary embolism, even when the specificity seems rather high (Sasahara et al., 1979; Hill et al., 1983b). Our results on perfusion defects in paper VII must therefore be interpreted with some caution.

RESULTS

Details in results are given within each paper (I-VIII) and will only be summarized here.

PAPER I

Dextran 70 increased cardiac output and decreased resistance in both systemic and pulmonary vessels. Volume blood flow in the femoral vein increased. Haematocrit was reduced. Dihydroergotamine increased pressure recordings, total peripheral resistance increased, but pulmonary vascular resistance remained unchanged. Cardiac output was unchanged, and the heart rate was reduced. In combination they resulted in a slight further increase in the pressure recordings, otherwise haemodynamics were largely unaffected.

Comments

In agreement with our findings dextran 70 is known to increase plasma volume, decrease peripheral resistance, increase arterial and venous volume blood flow (for review see Zederfeldt, 1965; Thorén, 1978). Much attention has been focused on the reduced viscosity and improved microcirculation achieved with the use of dextran (Gelin, 1956; Hint, 1964; Giuntini et al., 1966; Messmer, 1975).

Increased pressures were recorded after dihydroergotamine treatment. This is in accordance with other investigations (for review on the central haemodynamic effects of dihydroergotamine see Clark et al. (1978)).

With dextran 70 and dihydroergotamine combined only a slight further increase in recorded pressures was seen, and cardiac performance was only minimally changed. Though theoretically the combination of an α -receptor blocking agent and a plasma volume increase could result in an unacceptable increase in pressures and an increased work-load for the heart, no major adverse reac-

tions of this kind were found. The results thus permitted clinical evaluation of the combination.

PAPER II

Dextran 70 resulted in a general increase in tissue blood flow to most organs. Dihydroergotamine reduced tissue blood flow to pancreas and thyroid and increased the flow to the CNS. By the combination no adverse effects on distribution were seen.

Comments

Tissue blood flow has not previously been evaluated in a hypervolaemic situation, achieved by dextran 70. Blood flow to most tissues increased. Dihydroergotamine increased tissue blood flow to the CNS, a finding also observed in experiments on cats (Arvidsson et al., 1983).

PAPER III

Peripheral haemodynamic evaluation showed that dextran 70 increased arterial volume blood flow both during reactive hyperaemia and in rest, but did not affect calf vein clearance. Dihydroergotamine decreased reserve vein volume (blood pooling), and the venous emptying rate, measured plethysmographically. Arterial volume blood flow decreased. The venous blood flow velocity increased due to reduced venous area. Arterial vessel area was unchanged. Clearance of calf veins was not improved by dihydroergotamine. The combination of dextran 70 and dihydroergotamine produced no major improvement in venous circulation.

Comments

Our data on dihydroergotamine and its effect on the velocity of venous blood flow, which increased, is in agreement with earlier findings (Reickert, 1971; Mühe et al., 1975; Kunz et al., 1981). The reduced reserve vein volume and decreased venous vessel area agree with the findings of plethysmographic and phlebographic

studies (Mellander & Nordenfelt, 1970; Felix & Louven, 1972; Kakkar, 1981b). The slightly reduced arterial volume blood flow found has also been noted by others (Zimpfer et al., 1981; Raberger et al., 1981). There was no increase in clearance from calf veins after administration of dihydroergotamine, neither with contrast nor with isotope measurements.

Dextran increased arterial volume blood flow measured plethysmographically, which is in agreement with earlier findings (Schwartz et al., 1964; Gottstein et al., 1970; Humphreys et al., 1976; Yates et al., 1979; Gustavsson et al., 1981). In animal experiments, both venous volume blood flow and muscle tissue blood flow increased (I, II). Despite these alterations, clearance time from the calf veins was unaltered. In earlier studies of the effects of dextran, less attention has been focused on peripheral venous haemodynamics (Zederfeldt, 1965; Jansen, 1972) than on its rheologic advantages - reduced viscosity and blood shear rate (Gelin, 1956 & 1959; Appelgren & Lewis, 1970).

The combination of dextran and dihydroergotamine gave no additive flow promoting effect (II). To some extent the addition of dihydroergotamine seems to block the normal effects of dextran. The increased peripheral resistance brought about by dihydroergotamine may impair the microcirculatory effects of dextran.

PAPER IV

The pharmacokinetic evaluation showed a rapid absorption and a two phase plasma disappearance for subcutaneously administered dihydroergotamine. Dihydroergotamine had a slight tendency to accumulate during the first few days. Dextran concentrations in plasma showed an increase during infusion followed by a slow decline. When used in combination with dihydroergotamine, dextran levels were significantly higher (about 2 g/l) than when only dextran was given.

Comments

The pharmacokinetics of dihydroergotamine has not previously been investigated as far as subcutaneous administration is concerned, until recently (Schran et al., 1983). No studies of a multiple dose model has been performed.

For subcutaneously administered dihydroergotamine, the pharmacokinetic evaluation showed a rapid absorption and a two-phase decrease which is in accordance with findings for other methods of administration (Little et al., 1982), and also recent data of subcutaneous administration (Schran et al., 1983). Simulated curves and through levels in the multiple dose study gave plasma concentrations where dihydroergotamine will induce vasoconstriction (Müller-Schweinitzer, 1980; Aellig, 1981). There was an increase in dextran plasma concentrations during infusion, followed by a slow decline. This is similar to earlier findings (Åberg et al., 1977). The results of the multiple dose study indicate that, during a 48-hours interval, dextran concentrations will remain at an effective level.

With the combination of dextran and dihydroergotamine, no pharmacokinetic alterations were noted in the single dose study, but in the multiple dose study dextran concentrations were increased as compared with the group receiving dextran only. A similar finding has been reported in investigations of heparin combined with dihydroergotamine, where increased heparin concentrations were found in the combination therapy group (Kakkar et al., 1979; Popov-Cenic et al., 1981), though others have not been able to verify these findings, even in multiple dose studies (Beerman & Lahnborg, 1980; Briel et al., 1980).

PAPER V

Platelet aggregation in vitro induced by adrenaline was inhibited by dihydroergotamine, when concentrations were well above those obtained in plasma with clinically relevant dosages. No major effect on platelet function, coagulation or fibrinolysis

was found in the healthy volunteers, neither was any effect on fibrinolysis seen in the dogs. Haematocrit increased after dihydroergotamine administration.

Comments

In in vitro experiments dihydroergotamine has been shown to decrease platelet activity in rabbits (Barthel & Markwardt, 1974). Recently it has been shown that dihydroergotamine decreases the release from platelet α -granules (platelet factor 4 and β -thromboglobulin) (Kakkar, 1981b). In our study of healthy volunteers, no interaction with the platelet function ex vivo could be verified after clinically relevant doses of dihydroergotamine had been given. This is in agreement with findings by Vinazzer (1981). The dihydroergotamine concentrations necessary to inhibit adrenaline induced platelet activity in vitro was a hundred times greater than those arrived at by clinically relevant doses. Furthermore platelet activity evaluated in vivo by transection of microvessels in the rabbit mesentery, or platelet embolism after laser induced arteriole injury in rabbit ear chambers, was unaffected by dihydroergotamine (Bergqvist et al., 1983). Thus dihydroergotamine seems to have no major effect on platelets.

The coagulation variables followed were unchanged, at least after correction have been made for the haematocrit alteration. Fibrinolytic variables were also unaltered. These findings confirm other workers (Vinazzer, 1981; Popov-Cenic et al., 1981; Lindblad et al., in manuscript), but are in contrast to Svanberg et al. (1980) and Kakkar (1981b), where increased antithrombin III concentrations after dihydroergotamine administration was claimed or found.

Dihydroergotamine did not result in an increase in fibrinolytic activity. The increased blood pressure achieved within the pulmonary circulation by dihydroergotamine might theoretically induce plasminogen activator release. The pulmonary vessels have a high content of plasminogen activators, but no release of

plasminogen activators could be detected.

PAPER VI

In the thromboprophylactic study, dextran 70 on its own was as effective as when combined with dihydroergotamine in general surgery patients and elective hip surgery patients. The combination was significantly more effective than dextran 70 alone in emergency hip surgery patients. No side effects from the prophylactic treatment were seen.

PAPER VII

The thromboprophylactic effect of dihydroergotamine combined with low-dose heparin was as effective as a sulphated polysaccharide (PZ68) in elective general and urologic surgery and in hip surgery. The combination was better than dextran 70 regarding thrombotic complications in elective surgery, and comparable to dextran 70 in emergency hip surgery. In elective hip surgery patients, there was no difference in lung perfusion defects. The frequency of bleeding complications was low in patients given dextran 70 and those given dihydroergotamine in combination with low-dose heparin, and significantly higher in those given sulphated polysaccharide (PZ68) at the dosage used (100 mg/12 h).

PAPER VIII

In general surgery patients given dextran 70, there was a significant decrease in the frequency of thrombosis in legs furnished with compression stockings (0 %) compared with "unstockinged" legs (10 %). The combination was thus superior to dextran 70 on its own.

GENERAL DISCUSSION

The rational for using combination prophylaxis in patients undergoing surgery seems well-founded due to the multiplicity of factors involved in the pathogenesis of deep vein thrombosis postoperatively.

The results of combination prophylaxis, reviewed earlier (p 27) and are summarized in table VII.

Table VII

The thromboprophylactic effects of some combination prophylactic methods.

Type of combination	Effect of combination	
	General surgery	Hip surgery
Acetyl salicylic acid + dipyridamole	+	
Low-dose heparin + acetyl salicylic acid	+	?
Low-dose heparin + dihydroergotamine	+	+
Low-dose heparin + graded compression stockings	+	
Low-dose heparin + intermittent calf compression	0	
Dextran 70 + intermittent calf compression	0	
Dextran 70 + oral anticoagulation		(+)
Dextran 40 + low-dose heparin		0

In this investigation three types of combination prophylaxis were evaluated: dihydroergotamine + dextran 70, dihydroergotamine + low-dose heparin and graded compression stockings + dextran 70. In order to be able to make the clinical investigation on the efficiency of the combination of dextran 70 and dihydroergotamine, both affecting haemodynamics, investigations concerning the haemodynamic and pharmacokinetic effects were necessary. Further evaluation of the mechanism of action of dextran 70 and dihydroergotamine was also considered of interest.

The studies on central haemodynamics and on tissue blood flow showed no adverse reactions of the combination of dextran 70 and dihydroergotamine. The pharmacokinetic evaluation showed increased dextran concentrations in the multiple dose study, but otherwise, no interaction between the substances was seen. A clinical evaluation therefore was considered possible.

Dextran 70 increased tissue blood flow to most organs. Volume blood flow increased both in femoral vein (I, III) and artery (III). No evaluation of the effects of dextran 70 on platelets, coagulation and fibrinolysis was made, since such effects so extensively earlier have been investigated (Åberg, 1978; Carlin, 1980). It seems as changes in microcirculation and effects on platelets, coagulation and fibrinolysis are the main action of dextran 70 in thromboprophylactic treatment.

Dihydroergotamine decreased reserve vein volume and increased venous blood flow velocity (III). No major interaction with platelets, coagulation or fibrinolysis were found. The peripheral haemodynamic effects of dihydroergotamine seems to be responsible for the beneficial effect of dihydroergotamine in thromboprophylactic treatment.

In the first clinical study (VI), comparison was made between dextran 70 treatment alone and in combination with dihydroergotamine. A group undergoing emergency general surgery was added to the groups of patients undergoing elective general surgery, elective hip surgery, and hip fracture surgery. A somewhat hig-

her frequency of deep vein thrombosis in the first group compared with elective general surgery patients, has been reported (Webb et al., 1981). Their frequency of 35% indicate the importance of that patients undergoing emergency general surgery should receive thromboembolic prophylactic treatment.

The study was made as a tri-centric trial. Modern diagnostic equipment was available at all three centres and diagnostic routines were uniform. No additive effect was seen in general surgery patients, nor in elective hip surgery patients. However, in hip fracture patients the results of the combination were superior to those of dextran 70. Though the prophylactic effect of dextran 70 combined with dihydroergotamine in hip fracture patients needs confirmation. The prospect is an interesting one, since so far no prophylactic regime has proved superior to dextran 70-treatment in hip fracture patients.

The most obvious finding in this study was the discrepancy in thromboprophylactic effect by the combination of dihydroergotamine and dextran 70. In hip fracture patients an additive effect was seen, but there was lack of a potentiating effect in the other groups studied. This discrepancy is not easily explained but there are at least three factors which can be speculated on and which all speak in favour of an increased effect of dextran. First hip fracture patients had a lower average body weight than the other patients, thus hip fracture patients received a higher dextran concentration per kg body weight. It has been shown in hip surgery that the dextran dose is of importance (Evarts & Feil, 1970). Secondly hip fracture patients received their prophylaxis at diagnosis which meant 1.5 days before operation and it is known that the optimal dextran effect appears some hours after infusion (Åberg et al., 1977). Thirdly our pharmacokinetic study showed that when combined in multiple doses with dihydroergotamine dextran concentration increased by around 2 g/l (IV).

Possible explanations for the increased dextran concentration when simultaneous dihydroergotamine is given could be that pooled venous blood mobilized by dihydroergotamine has a higher

erythrocyte volume fraction, or that plasma volume is decreased. In both dogs (I) and man (V) haematocrit increases after dihydroergotamine administration. Increased capillary permeability, which may reduce plasma volume, has not been recorded with plethysmographic technique after dihydroergotamine administration (Mellander & Nordenfelt, 1970; Ulrich et al., 1973). The increase in central venous pressure achieved by dihydroergotamine (I, Lange & Echt, 1972) can affect renal function and may result in a decreased ADH-concentration which in turn will promote diuresis (Gauer, 1975). Unpublished results, where increased diuresis was found, support the existence of such an effect of dihydroergotamine. If indeed plasma volume is reduced, thereby increasing dextran or heparin concentrations, this could be one of the mechanisms responsible for the additive effect in thromboprophylaxis provided by dihydroergotamine.

In the second study (VII) the combination of dihydroergotamine and low-dose heparin, and a sulphated polysaccharide (PZ68), were both compared with dextran 70-treatment. Since dextran 70 is less effective in reducing deep vein thrombosis in elective general surgery cases no such comparison was made in those patients. Dextran 70 treatment was chosen for comparison because earlier studies in hip surgery patients had shown it to be more effective than low-dose heparin in reducing the extension of deep vein thrombosis (Bergqvist, 1983).

Low-dose heparin in combination with dihydroergotamine showed good prevention of thrombotic complications, even regarding "major thrombi", in patients undergoing elective surgery. In emergency surgery, low-dose heparin prophylaxis has been found less effective. Trauma initiates several alterations in coagulation, platelets and fibrinolysis. Since this activation hinders the formation of heparin-antithrombin III-complexes, coagulation is less inhibited by heparin when it is given after trauma (Dryjski et al., 1983). In our study the prophylactic effect of low-dose heparin and dihydroergotamine was similar to that of dextran 70-treatment in hip fracture patients. In a study by Lahnborg (1980), no additive effect of dihydroergotamine to low-dose

heparin prophylaxis was seen in hip fracture patients. The beneficial and additive effects of dihydroergotamine and low-dose heparin in elective surgery have been reviewed previously (p 22) and our findings confirm this, and that a better thromboprophylactic effect is provided by this combination than by dextran 70 in elective hip surgery.

The sulphated polysaccharide (PZ68) (VII) promotes antifactor X-activity but does not interact as much as heparin with other serine proteases such as thrombin (Bergqvist & Nilsson, 191; Ryde et al., 1981). This suggests an effect different from that of heparin. At least theoretically, reduced bleeding complications would be expected. Our findings with a dose of 100 mg PZ68 given twice daily showed a good thrombo-prophylactic effect in elective surgery, and a similar effect to that of dextran 70 in hip fracture surgery. The incidence of bleeding complications was, however, unacceptably high. With a lower dose (75 mg x 2) the same good prophylactic effect has been found in elective general surgery (Bergqvist & Ljungnér, 1981), and an effect similar to that of dextran 70 in hip fracture patients (Fredin et al., 1982). In neither of these studies was there any tendency for increased bleeding complication.

In patients undergoing elective hip surgery (VII), perfusion scintigraphy was carried out. The frequency of perfusion defects was found to be 11-18%, results being similar between the groups. Despite prophylactic treatment, there were three cases of fatal pulmonary emboli. It was remarkable that the differences in frequency of deep vein thrombosis did not result in differences in the number of lung perfusion defects. The reason for this could be due to that even if there is a higher frequency of pulmonary embolism in dextran 70 treated patients, the increased lysisability during dextran treatment may more promptly give lysis compared to patients in the other treatment groups. When the lung perfusion scintigraphy was made, some emboli could have been lysed, and probably this would occur with a higher frequency in dextran treated patients, and thus not diagnosed.

In the third study (VIII), the combination of dextran 70 and graded elastic compression stockings was evaluated and compared with treatment using dextran 70 on its own. In order to ensure comparable risk factors, it was decided to choose which of a patient's legs was to be supplied with a stocking by random order, the other serving as a control. All patients received dextran 70. In a haemodynamic study it has been found that venous circulation are slightly improved even in the leg not subjected to compression (Spiro et al., 1970); this finding does not, however, render our findings inconclusive.

The combination of dextran 70 and a graded compression stocking showed an additive effect in general surgery patients. Further studies are needed but the results are most encouraging.

An additive effect of low-dose heparin combined with graded compression stockings has been reported (Törnngren, 1980).

In two studies, dextran 70 has been combined with intermittent calf compression without any additive effect being found (Browse et al., 1976; Smith et al., 1978). Neither has the combination of low-dose heparin and intermittent calf compression been shown to be additive (Roberts & Cotton, 1975). The results are hard to explain since intermittent calf compression has been shown to be effective in the clearance of calf veins, and to increase venous volume blood flow. One reason could be that the high compression (usually 40 mm Hg) has a detrimental effect on the microcirculation, and another that intermittent calf compression brings about "pendular" shifts in venous blood flow. Sequential intermittent calf compression might therefore be a better alternative (Nicolaides et al., 1980). Such an additive effect was recently found for low-dose heparin and sequential intermittent calf compression (Kakkar, personal communication).

The use of compression stockings has been shown to improve venous flow velocity and clearance of calf veins (Partsch & Kahn, 1982; Lewis et al., 1976). Dextran affects haemostasis and microcirculation, but seems not to improve venous calf clearance.

Thromboprophylactically the combination of graded compression stockings improving clearance and dextran 70 has an additive effect.

All prophylactic methods have drawbacks. Heparin treatment causes bleeding complications and response to heparin administration differs individually (Salzman & Davies, 1980); this is probably due to the binding of heparin to a histidine rich glycoprotein (Jacobsson et al., 1983; Lijnen et al., 1983). Heparin has a higher affinity for binding to this glycoprotein than to antithrombin III and since the plasma concentrations of this histidine rich glycoprotein varies and even decreases postoperatively, the anticoagulant effect of heparin will also vary (Lijnen et al., 1983).

Dextran treatment occasionally causes anaphylactic reactions, but this has been effectively reduced by the use of pretreatment with hapten dextran (Ljungström, 1983). Nonetheless, the risk of volume overloading and renal complications must be considered (Bergqvist, 1983). Moreover the effects of dextran on haemostasis must be taken into consideration. Moreover, the incidence of bleeding complications has been reported to be the same as for low-dose heparin treatment (Bergqvist, 1983).

In 30 cases reported to the manufacture (Krupp, personal communication, seven reported in literature) dihydroergotamine has been reported to cause vasospasm. All these cases, however, had severe postoperative complications, many of which may well cause vasospasm. We found a very slight reduction in arterial volume blood flow (III), but in border-line cases also a slight reduction could be harmful. If vasospasm develops, dihydroergotamine treatment must be interrupted. The effect of dihydroergotamine on the coronary vascular bed has also been discussed. In controlled studies, no increased risk of myocardial affection has been noted (Gruber, 1982; Breddin et al., 1983; Lindblad, 1983), and no reports on induction of myocardial ischaemia or infarction have been presented, despite the extensive use of dihydroergotamine combined with low-dose heparin in several countries.

Moreover tissue blood flow to the heart was unchanged (II), and recently it has been shown that dihydroergotamine even reduces ischaemic area and lactate metabolism after experimental occlusion of a coronary artery (Raberger et al., 1983).

Several external compression methods have been found to reduce thrombosis development, at least in general surgery patients. These methods do not affect haemostasis. It has been proposed that intermittent compression will induce increased circulating fibrinolytic activity (Knight & Dawson, 1976; Stevenson et al., 1977; Tarnay et al., 1980; Caprini et al., 1983), but other well-made investigations seem to have ruled out such an effect also in the case of graded compression stockings (Browse et al., 1977; Ljungnéer et al., 1981). The major drawback of compression methods seems to be discomfort to the patient. The method used must of course be tolerable.

To sum up, some combination regimens have an additive thromboprophylactic effect. Even though the incidence of thrombotic complications is effectively reduced, the methods used in our studies are not optimal and future studies must aim at reducing postoperative thromboembolic complications even more.

CONCLUSIONS

Studies on dihydroergotamine and dextran 70

In dogs dextran 70 increased cardiac output, but blood pressure was unchanged. Dihydroergotamine induced increased systemic arterial, pulmonary artery, central venous pressure, and peripheral resistance while pulmonary vascular resistance was unchanged.

Dextran 70 increased tissue blood flow in most organs in parallel to the increased cardiac output. Dihydroergotamine decreased tissue blood flow to pancreas and thyroid, and increased tissue blood flow to CNS.

The combination of dextran 70 and dihydroergotamine induced no changes which could not be foreseen from the effects of the single drug, or which could be potentially harmful when the drugs are used clinically.

In humans dihydroergotamine reduced reserve vein volume, increased venous blood flow rate but the clearance from calf veins was unchanged. Dextran 70 increased venous volume blood flow but did not change clearance from calf veins. The combination did not interfere with any effects on peripheral haemodynamics which could be more beneficial from a thromboprophylactic point of view than either drugs used separately.

A pharmacokinetic study of subcutaneously administered dihydroergotamine showed a rapid absorption followed by a twophase decrease in plasma concentrations. When it was combined with dextran 70, the dextran concentrations were uninfluenced in a single dose study, whereas in a multiple dose study dextran concentrations were significantly increased.

Dihydroergotamine inhibited platelet aggregation in vitro in a dose dependent way but only in doses far above clinically relevant. In clinical doses dihydroergotamine did not affect plate-

lets, coagulation or fibrinolysis.

In hip fracture patients the combination of dihydroergotamine and dextran 70 significantly reduced the frequency of thrombosis as compared with dextran 70 alone, the effect probably being due to an increased dextran effect in this group of patients. In patients undergoing general surgery and elective hip surgery the combination had no better effect than dextran alone.

Study on dihydroergotamine and low-dose heparin

Dihydroergotamine and low-dose heparin in fix combination was equally effective as the sulphated polysaccharide, sodium pentosan polysulphate, to prevent postoperative thrombosis in patients undergoing elective general surgery, elective hip surgery and hip fracture surgery, but gave rise to significantly less bleeding complications. In elective hip surgery it was more effective than dextran 70 and in hip fracture patients it was as effective.

Study on graded compression stockings and dextran 70

Addition of an individually fitted graded elastic compression stocking to one leg in patients with a basic prophylaxis with dextran 70 gave a significant reduction in the frequency of postoperative thrombosis after general surgery compared with the unstockinged leg.

The multifactorial nature of postoperative thrombosis makes it logical to investigate combined prophylactic methods with influence on different pathogenetic factors. This study shows three combination regimens which are effective, and also indicates that different regimens have their optimal effect in different clinical situations.

REFERENCES

- Åberg M. On effect of dextran on lysability and structure of ex vivo thrombi, platelet function and factor VIII. Thesis, University of Lund, 1978.
- Åberg M, Arfors K-E, Bergentz S-E. Effect of dextran on factor VIII and thrombus stability in humans. Significance of varying infusion rates. *Acta Chir Scand* 1977, 143:417.
- Åberg M, Nilsson IM, Hedner U. Antithrombin III after operation. *Lancet* 1973, II:1337.
- Aellig WH. A new technique for recording compliance of human hand veins. *Br J Clin Pharmacol* 1981, 11:237.
- Ah-See AK, Arfors K-E, Bergqvist D, Dahlgren S. The haemodynamic and antithrombotic effects of intermittent pneumatic calf compression on femoral vein blood flow. A comparison between different pump types. *Acta Chir Scand* 1976, 142:381.
- Allan A, Williams JT, Bolton JP, Le Quesne LP. The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. *Br J Surg* 1983, 70:172.
- Almén T, Nylander G. Serial phlebography of the normal lower leg during muscular contraction and relaxation. *Acta Radiol* 1962, 57:264.
- Appelgren KL, Lewis DH. Capillary flow and capillary transport in dog skeletal muscle after induced intravascular RBC aggregation and disaggregation. *Europ Surg Res* 1970, 2:161.
- Arendrup H, Toftgaard C. Lavdosis-heparinbehandling. En undersøgelse af de lokale virkninger af 5.000 IE natriumheparin og calciumheparin. *Ugeskr Laeg* 1979, 141:1203.
- Arvidsson S, Bergqvist D, Esquivel C, Lindblad B, Haglund U. Hemodynamic effects of dihydroergotamine and ketanserin in E-coli bacteriemic shock. *Scand J Clin Invest* 1983, S 164:14.
- Arvidsson S, Bergqvist D, Haglund U, Lindblad B. Cardiac output measurements with thermodilution and radioactive microspheres. A comparative study in cats. *Scand J clin Lab Invest*, in press.
- Barthel W, Markwardt F. Aggregation of blood platelets by biogenic amines and its inhibition by antiadrenergic and anti-serotonergic agents. *Biochem Pharmacol* 1974, 23:37.
- Becker J, Schampi B. The incidence of postoperative venous thrombosis of the legs. A comparative study on the prophylactic effect of dextran 70 and electrical calf-muscle stimulation. *Acta Chir Scand* 1973, 139:357.
- Beerman B, Lahnborg G. Pharmacokinetics of heparin in healthy and obese subjects and in combination with dihydroergotamine. *Thromb Haemost* 1981, 45:24.

- Bergentz S-E. Dextran in the prophylaxis of pulmonary embolism. *World J Surg* 1978, 2:19.
- Bergentz S-E, Nilsson IM. Effect of trauma on coagulation and fibrinolysis in dogs. *Acta Chir Scand* 1961, 122:21.
- Bergqvist D. Postoperative thromboembolism. Frequency, Etiology, Prophylaxis. Springer-Verlag, Berlin, Heidelberg, New York. 1983.
- Bergqvist D, Arfors K-E. Haemostasis in the microvasculature of the rabbit mesentery; Effects of some pharmacological agents of current interest in haemostasis and thrombosis. *Haemostasis* 1976, 5:74.
- Bergqvist D, Arvidsson S, Esquivel CO, Lindblad B, Haglund U. The effect of serotonin inhibition on initial microvessel hemostasis and platelet aggregation in vivo. *Thromb Haemostas*, 1983, 49:173.
- Bergqvist D, Hedner U, Sjörin E, Holmer E. Anticoagulant effects of two types of low molecular weight heparin administered subcutaneously. *Thromb Res*, in press.
- Bergqvist D, Ljungné H. A comparative study of dextran 70 and a sulphated polysaccharide in the prevention of postoperative thromboembolic complications. *Br J Surg* 1981, 68:449.
- Bergqvist D, Ljungné H, Nilsson M. Venous emptying from the calf. Methodological report and effect of intermittent pneumatic compression. *Acta Chir Scand* 1982, 148:669.
- Bergqvist D, Nilsson IM. A sulphated polysaccharide - the effects in vivo and in vitro on the haemostatic system in healthy volunteers. *Thromb Res* 1981, 23:309.
- Bloom AL, Giddings JC, Wilks CJ. Factor VIII on the vascular intima: possible importance in haemostasis and thrombosis. *Nature New Biology* 1973, 241:217.
- Borgström S, Gelin L-E, Zederfeldt B. The formation of vein thrombi following tissue injury. *Acta Chir Scand* 1959, Suppl 247.
- Born GVR, Bergqvist D, Arfors K-E. Evidence for inhibition of platelet activation in blood by a drug effect on erythrocytes. *Nature* 1976, 259:233.
- Breddin K, Häring R, Koppenhagen K. Prävention postoperativer thrombotischer Komplikationen mit Heparin und Dihydroergotamin. *Dtsch Med Wochenschr* 1983, 108:98.
- Briel R. Plasma heparin levels during and after hysterectomy with low-dose heparin or heparin-dihydroergotamin prophylaxis. *Thromb Res* 1980, 19:513.

- Browse NL, Clemenson G, Bateman NT, Gaunt JI, Croft DN. Effect of intravenous dextran 70 and pneumatic leg compression on incidence of postoperative pulmonary embolism. *Br Med J* 1976, 2:1281.
- Browse NL, Gray L, Morland M. Changes in blood fibrinolytic activity after surgery (the effect of deep vein thrombosis and malignant disease). *Br J Surg* 1977, 64:23.
- Caen JP, Nurden AT, Jeanneau C, Michel H, Tobelem G, Levy-Toledano S, Sultan Y, Valensi F, Bernard J. Bernard-Soulier syndrome: a new platelet glycoprotein abnormality. Its relationship with platelet adhesion to subendothelium and with the factor VIII von Willenbrand protein. *J Lab Clin Med* 1976, 87:586.
- Canfield W, Neshiem M, Kisiel W, Mann K. Proteolytic inactivation of bovine factor Va by bovine activated protein C. *Circulation* 1978, 58:Suppl II:210.
- Caprini JA, Chucker JI, Zuckerman L, Vagher JP, Franck CA, Cullen JE. Thrombosis prophylaxis using external compression. *Surg Gynecol Obstet* 1983, 156:599.
- Carlin G. Effect of dextran on fibrinolysis. Thesis, University of Uppsala. 1980.
- Cash J. Neurohumoral pathways associated with the release of plasminogen activator in man. In: Davidson JF, Samama M, Desnoyers PC. Progress in chemical fibrinolysis and thrombolysis. Raven Press. New York, 1975, vol. 1:97.
- Castellino FJ, Violand BN. The fibrinolytic system - basic considerations. *Prog Cardiovasc Dis* 1979, 21:241.
- Cazenave J-P, Benveniste J, Mustard JF. Aggregation of rabbit platelets by platelet-activating factor is independent of the release reaction and the arachidonate pathway and inhibited by membrane-active drugs. *Lab Invest* 1979, 41:275.
- Clark B, Chu D, Aellig WH. Actions on the heart and circulation. In: Berde B, Schild HO (eds). Ergot alkaloids and related compounds. Springer, Berlin, Heidelberg, New York, 1978.
- Clark C, Cotton LT. Blood flow in deep veins of legs. Recording technique and evaluation of methods to increase flow during operation. *Br J Surg* 1968, 55:211.
- Collen D. Identification and some properties of a new-fast-reaching plasma inhibitor in human plasma. *Eur J Biochem* 1976, 69:209.
- Collen D, Stassen JM, Verstraete M. Thrombolysis with human extrinsic (tissue type) plasminogen activator in rabbits with experimental jugular vein thrombosis. Effect of molecular form and dose of activator, age of the thrombus and route of administration. *J Clin Invest* 1983, 71:368.

- Comp PH, Esmon CT. Generation of fibrinolytic activity by infusion of activated protein C into dogs. *J Clin Invest* 1981, 68:1221.
- Cope C, Reyes T, Skversky N. Phlebographic analysis of the incidence of thrombosis in hemiplegia. *Radiology* 1973, 109:581.
- Crafoord C, Jorpes E. Heparin as a prophylactic against thrombosis. *JAMA* 1941, 116:2831.
- Czechanowski B, Heinrich F. Prophylaxe venöser Thrombosen bei frischem ischämischem zerebrovaskulärem Insult. Doppelblindstudie mit Heparin-Dihydergot. *Dtsch Med Wochenschr* 1981, 106:1254.
- Czervionke RL, Hoak JC, Fry GL. Effect of aspirin on thrombin induced adherence of platelets to cultured cells from the blood vessel wall. *J Clin Invest* 1978, 62:847.
- De Gaetano. Platelets, prostaglandins and thrombotic disorders. In: Prentice CRM (ed). *Thrombosis, Clinics in haematology*. Vol 10:2, 1981:297.
- Doran FSA, Drury M, Sivyer A. A simple way to combat the venous stasis which occurs in the lower limbs during surgical operations. *Br J Surg* 1964, 51:486.
- Dormandy J, Edelman J. High blood viscosity: an aetiological factor in venous thrombosis. *Br J Surg* 1973, 60:187.
- Dryjski M, Olsson P, Swedenborg . Inhibition of thrombin activity appearing on the vascular wall after trauma. *Thromb Haemost* 1983, 50:69.
- Evarts C, Feil E. Prevention of thromboembolic disease after elective surgery in the hip. *J Bone Joint Surg* 1971, 53:1271.
- Esquivel CO, Bergqvist D, Björck C-G, Nilsson B. Comparison between commercial heparin, low molecular weight heparin and pentosan polysulfate on hemostasis and platelets in vivo. *Thromb Res* 1982, 28:389.
- Felix R, Louven B. Zur Vasoaktivität von Dihydroergotamin. Phlebographische Untersuchungen. *Fortschr Med* 1972, 90:757.
- Flicoteaux H, Kher A, Jean N, Blary M, Judet T, Honnart F, Pâsteyer J. Comparison of low dose heparin and low dose heparin combined with aspirin in prevention of deep vein thrombosis after total hip replacement. *Pathol Biol* 1977, 25:55.
- Fredin HO, Nillius SA, Bergqvist D. Prophylaxis of deep vein thrombosis in patients with fractures of the femoral neck. A prospective comparison between dextran and a sulphated polysaccharide. *Acta Orthop Scand* 1982, 53:413.
- Gallus AS, Hirsch J, Gent M. Relevance of preoperative and postoperative blood tests to postoperative leg-vein thrombosis. *Lancet* 1973, II:805.

- Gallus AS, Raman K, Darby T. Venous thrombosis after elective hip replacement - the influence of preventive intermittent calf compression and of surgical technique. *Br J Surg* 1983, 70:17.
- Gauer OH. Moderator's introduction. *Cardiology* 1976, 61:Suppl 1:2.
- Gelin L-E. Studies in anemia of injury. *Acta Chir Scand* 1956, Suppl. 210.
- Gelin L-E. The significance of intravascular aggregation following injury. *Bull soc internat chir* 1959, 18:4.
- Gibbard FC, Gould SR, Marks P. Incidence of deep vein thrombosis and leg oedema in patients with strokes. *J Neurol Neurosurg Psychiatry* 1976, 39:1222.
- Giercksky K-E, Österud B, Andersen O, Revhaug A, Gaudernack G. Dissiminated intravascular coagulation (DIC) triggered by pro-coagulant active leucocytes. *Acta Chir Scand* 1983, Suppl 516: 42.
- Giuntini C, Maseri A, Bianchi M. Pulmonary vascular distensibility and lung compliance as modified by dextran infusion and subsequent atropine injection in normal subjects. *J Clin Invest* 1966, 45:1770.
- Gottstein U, Sedlmeyer I, Schöttler M, Gülk V. Der Effekt von niedermolekularem Dextran auf die Unterschenkel durchblutung von Gesunden und von Kranken mit peripheren Arteriellen Zirkulationsstörungen. *Dtsch Med Wochenschr* 1970, 95:1955.
- Griffin JH, Mosher DF, Zimmerman TS, Kleiss AJ. Protein C, an antithrombotic protein, is reduced in hospitalized patients with intravascular coagulation. *Blood* 1982, 60:261.
- Gruber UF. Prevention of fatal postoperative pulmonary embolism by heparin dihydroergotamine or Dextran 70. *Br J Surg* 1982, 69:S 54.
- Gruber UF, Saldeen T, Brokop T, Ekelöf B, Eriksson I, Goldie I, Gran L, Hohl M, Jonsson T, Kristersson S, Ljungström KG, Lund T, Maartman Moe H, Svensjö E, Thomson D, Torhorst J, Trippestad A, Ulstein M. Incidences of fatal postoperative pulmonary embolism with dextran 70 and low-dose heparin: an international multicentre study. *Br Med J* 1980, 280:69.
- Grönwall A, Ingelman B. Untersuchungen über Dextran und sein Verhalten bei parenteralen Zufuhr. I. *Acta Physiol Scand* 1944, 7:97.
- Gustavsson L, Appelgren L, Myrvold HE. Blood flow and in vivo apparent viscosity in working and non-working skeletal muscle of the dog after high and low molecular weight dextran. *Circ Res* 1981, 48:465.

- Harris WH, Raines J, Athanasoulis C, Waltman E, Salzman E. External pneumatic compression versus warfarin in reducing thrombosis in high-risk patients. In: Madden J, Hume M (eds). Venous thromboembolism. Prevention and treatment. Appleton-Century-Crafts, New York. 1976:51.
- Harris WH, Salzman EW, Athanasoulis C, Waltman AC, Baum S, DeSanctis RW. Comparison of warfarin, low-molecular weight dextran, aspirin and subcutaneous heparin in prevention of venous thromboembolism following total hip replacement. *J Bone Joint Surg* 1974, 56A:1552.
- Hartman JD, Pugh JL, Smith RD, Robertson Jr WW, Yost RP, Janssen HF. Cyclic sequential compression of the lower limb in prevention of deep venous thrombosis. *J Bone Joint Surg* 1982, 64A:1059
- Havig Ö. Deep vein thrombosis and pulmonary embolism. An autopsy study with multiple regression analysis of possible risk factors. *Acta Chir Scand* 1977, Suppl. 478.
- Hedner U, Collen D. Immunochemical distinction between the inhibitors of plasminogen activation and antiplasmin in human plasma. *Thromb Res* 1976, 8:875.
- Hedner U, Martinsson G. Inhibition of activated Hageman factor (Factor XIIa) by an inhibitor of plasminogen activation (PA inhibitor). *Thromb Res* 1978, 12:1015.
- Hedner U, Martinsson G, Bergqvist D. Influence of operative trauma on factor XII and inhibitor of plasminogen activator. *Haemostasis* 1983, 13:219.
- Hedner U, Nilsson IM. The role of fibrinolysis. In: Prentice CRM (ed). *Thrombosis. Clinics in haematology*. WB Saunders Comp, London, Philadelphia, Toronto. 1981, Vol. 10/2:327.
- Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide-labelled particles. *Progr Cardiovasc Dis* 1977, 20:55.
- Hint H. The flow properties of erythrocyte suspensions in isolated rabbit's ear, the effects of erythrocyte aggregation, hematocrit and perfusion pressure. *Bibl Anat* 1964, 4:112.
- Hodgson DC. Venous stasis during surgery. *Anaesthesia* 1964, 19:96.
- Holmberg L, Mannucci PM, Turesson I, Ruggeri ZM, Nilsson IM. Factor VIII antigen in the vessel walls in von Willebrand's disease and haemophilia A. *Scand J Haematol* 1974, 13:33.
- Hornstra G. Prostanoids and their precursor fatty acids in the management of arterial thrombosis. In: *Progress in Pharmacology* Gustav Fischer Verlag, Stuttgart, New York. 1982:vol. 4/4:75.

Howard MA, Montgomery DC, Hordisty RM. Factor VIII-related antigen in platelets. *Thromb Res* 1974, 4:617.

Hull R, Carter C, Turpie AG, Jay R, Hirsch J, Kinch D, Raskob G. A randomized trial of sequential pneumatic limb compression in the prevention of venous thromboembolism following elective hip surgery. *Thromb Haemost* 1983a, 50:66.

Hull R, Hirsch J. Advances and controversies in the diagnosis, prevention and treatment of venous thromboembolism. In: Brown EB (ed). *Progress in Hematology*. Grune & Stratton Inc. New York, 1981, Vol XII:73.

Hull R, Hirsch J, Carter C, Jay R, Coates G, Gill J, Turpie AGG. Pulmonary angiography, ventilation scanning and venography in patients with clinically suspected pulmonary embolism and abnormal perfusion scans. *Thromb Haemost* 1983b, 50:328.

Humphreys WV, Walker A, Cave FD, Charlesworth D. The effect of an infusion of low molecular weight dextran on peripheral resistance in patients with arteriosclerosis. *Br J Surg* 1976, 63:691.

Immelmann EJ, Jeffery P, Benatar SR, Elliot MS, Ferguson AD, Smith JS, Shepstone BJ, Funston MR, Jacobs P, Louw JH. The prevention of post-operative thrombo-embolic disease - a prospective trial. *International Vascular Symposium*, London, 1981, Abstract 073.

An international multicentre trial. Prevention of fatal postoperative pulmonary embolism by low doses of heparin. *Lancet* 1975, II:45.

Isacsson S, Nilsson IM. Defective fibrinolysis in blood and vein walls in recurrent "idiopathic" venous thrombosis. *Acta Chir Scand* 1972, 138:313.

Jansen H. Postoperative thromboembolism and its prevention with 500 ml dextran given during operation. With a special study of the venous flow pattern in the lower extremities. *Acta Chir Scand* 1972, Suppl. 427.

Jacobsson H, Högstorp H, Saldeen T. Posttraumatic variation of a plasminogen-binding and a non-plasminogen-binding from histidine rich glycoprotein in plasma. *Thromb Haemost* 1983, 50:300.

Joffe S. Drug prevention of postoperative deep vein thrombosis. A comparative study of calcium heparinate and sodium pentosan polysulfate. *Arch Surg* 1976, 111:37.

Johnsen ULH, Lyberg T, Galdal KS, Prydz H. Platelets stimulate thromboplastin synthesis in human endothelial cells. *Thromb Haemost* 1983, 49:69.

Jönsson G. Venous circulation in the lower half of the body. A clinico-experimental study with special reference to the postoperative phase. *Acta Chir Scand* 1951, Suppl. 161.

- Jorpes E. Om heparinets kemi och dess medicinska användbarhet. Hygiea 1936, 98:218.
- Kakkar VV. The current status of low-dose heparin in the prophylaxis of thrombophlebitis and pulmonary embolism. World J Surg 1978, 2:3.
- Kakkar VV. Prevention of venous thromboembolism. In: Prentice CRM (ed). Thrombosis. Clinics in haematology. WB Saunders Comp Ltd London, Philadelphia, Toronto. 1981a, Vol. 10;2:543.
- Kakkar VV. Knowledge and prospective of thromboembolic research. In: Tscherne H, Deutsch E (eds). Postoperative Thromboembolie-Prophylaxe aus aktueller Sicht. George Thieme Verlag, Stuttgart, New York. 1981b:1.
- Kakkar VV. Prevention of fatal post-operative pulmonary embolism (PE) by low doses of subcutaneous sodium (Na^+) or calcium (Ca^{++}) heparin - a double blind randomized multicentre trial. Thromb Haemost 1983a, 50:10.
- Kakkar VV. Prevention of post-operative venous thromboembolism by a low molecular weight heparin fraction. Thromb Haemost 1983b, 50:91.
- Kakkar VV, Lawrence D, Bentley PG, de Haas HA, Ward V, Scully MF. A comparative study of low doses of heparin and a heparin analogue in the prevention of postoperative deep vein thrombosis. Thromb Res 1978, 13:111.
- Kakkar VV, Stamatakis JP, Bentley PG, Lawrence D, de Haas HA, Ward VP. Prophylaxis for postoperative deep vein thrombosis. Synergistic effect of heparin and dihydroergotamine. JAMA 1979, 241:39.
- Karino T. Possible function of vortices as automatic traps and generators of thrombi. Thromb Haemost 1983, 50:68.
- Kemble JV. The effect of surgical operation on leg venous flow measured with radioactive hippuran. Postgrad Med J 1971, 47:773.
- Knight MTN, Dawson R. Effect of intermittent compression of the arms on deep venous thrombosis in the legs. Lancet 1976, II:1265.
- Koekenberg LJL. Experimental use of macrodex as a prophylaxis against postoperative thromboembolism. Exp Med Amst 1961, 40:123.
- Korvald E, Stören E, Ongre A. Simultaneous use of warfarin-sodium and dextran 70 to prevent post-operative venous thrombosis in patients with hip fractures. A controlled trial. J Oslo City Hosp 1973, 23:25.
- Kunz S, Burth OM, Zimmerer E. Assessment of venous function after major gynecological surgery with heparin-dihydroergotamine in the prophylaxis of DVT. Thromb Haemost 1981, 46:190.

- Laaksonen VO, Arola MKJ, Kivisaari A, Hannelin M. Effect of different modes of operative anaesthesia on the clearance time of 125-I-fibrinogen from calf veins. *Ann Chir Res* 1974, 6:356.
- Lahnborg G. Effect of low-dose heparin and dihydroergotamine on frequency of postoperative deep-vein thrombosis in patients undergoing post-traumatic hip surgery. *Acta Chir Scand* 1980, 146:319.
- Lange L, Echt M. Vergleichende Untersuchungen über venentonisierende Pharmaka. *Fortschr Med* 1972, 90:1161.
- Laurell C-B, Jeppsson J-O. Protease inhibitors in plasma. In: Putnam FW (ed). *The plasma proteins; structure, function and genetic control*. Academic Press, New York, San Francisco, London. 1975, vol. I:229.
- Leandoer L. Fibrinogen in blood and lymph after massive haemorrhage in dogs. *Acta Chir Scand* 1968, 134:511.
- Legrand YJ, Karniguian A, Le Francier P, Fauvel F, Caen JP. Evidence that a collagen-derived nonapeptide is a specific inhibitor of platelet-collagen interaction. *Biochem Biophys Res Commun* 1980, 96:1579.
- Lewis C, Antoine J, Mueller C, Talbot W, Swaroop R, Edwards S. Elastic compression in the prevention of venous stasis. A critical reevaluation. *Am J Surg* 1976, 132:739.
- Lewis C, Mueller C, Edwards S. Venous stasis on the operating table. *Am J Surg* 1972, 124:780.
- Liebermann GE, Lewis P, Peters TJ. A membrane-bound enzyme in the rabbit aorta capable of inhibiting adenosine diphosphate-induced platelet aggregation. *Lancet* 1977, II:330.
- Lijnen HR, van Hoef B, Collen D. Interaction of heparin with histidine-rich glycoprotein and with antithrombin III. *Thromb Haemost* 1983, 50:560.
- Lindblad B. Kliniska erfarenheter av Orstanorm med heparin. In: Bergqvist D (ed). *Aktuella synpunkter på postoperative tromboembolism*. Sandoz AB. Täby, Kirurgiska kliniken, Allmänna sjukhuset, Malmö. 1983:75.
- Lindblad B, Bergqvist D, Hallböök T, Lindhagen A, Hedner U. Haemostatic changes in surgical patients given thromboembolic prophylaxis with dextran 70 alone or in combination with dihydroergotamine. In manuscript.
- Lindström B, Ahlman H, Jonsson O, Sivertsson R, Stenqvist O. Blood flow in the calves during surgery. *Acta Chir Scand* 1977, 143:335.
- Little PJ, Jennings GL, Skews H, Bobik A. Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol* 1982, 13:785.

- Ljungnér H, Bergqvist D. Decreased fibrinolytic activity in the bottom of human vein valve pockets. VASA 1983, in press.
- Ljungnér H, Bergqvist D, Nilsson IM. Effect of intermittent pneumatic and graduated static compression on factor VIII and the fibrinolytic system. Acta Chir Scand 1981, 147:657.
- Ljungnér H, Bergqvist D, von Hebel I, Isacsson S. The influence of major surgery on plasminogen activator activity in superficial hand veins. Eur Surg Res 1983, 15:161.
- Ljungström KG. Prophylaxis of postoperative thromboembolism with dextran 70. Improvements of efficacy and safety. Thesis. Karolinska Institutet, Stockholm. 1983.
- Loew D, Brücke P, Simma W, Vinazzer H, Dienstl E, Boehme K. Acetylsalicylic acid, low dose heparin, and a combination of both substances in the prevention of postoperative thromboembolism. A double blind study. Thromb Res 1977, 11:81.
- Lollar P, Owen WG. Clearance of thrombin from the circulation by high-affinity binding sites on endothelium: Possible role in the inactivation of thrombin by antithrombin III. Circulation 1980, 62:Suppl III:278.
- Majno G, Joris I. Endothelium 1977: A review. Adv Exp Med Biol 1978, 104:169.
- Mannucci PM, Åberg M, Nilsson IM, Robertson B. Mechanism of plasminogen activator and factor VIII increase after vasoactive drugs. Br J Haematol 1975, 30:81.
- Mason R, Sharp D, Chuang H, Mohammed F. The endothelium. Roles in thrombosis and haemostasis. Arch Pathol Lab Med 1977, 101:61.
- Mc Lachlin AD, Mc Lachlin JA, Jory T, Rawling EG. Venous stasis in the lower extremities. Ann Surg 1960, 152:678.
- Mellander S, Nordenfelt I. Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. Clin Sci 1970, 39:183.
- Messmer K. Hemodilution. Surg Clin N Amer 1975, 55:659.
- Meyerowitz B, Nelson R. Measurement of the velocity of blood in in lower limb veins with and without compression. Surgery 1964, 56:481.
- Modig J, Malmberg P, Karlström G. Effect of epidural versus general anaesthesia on calf blood flow. Acta Anaesth Scand 1980, 24:305.
- Moncada S. Prostacyclin and thromboxane A₂ in the regulation of platelet-vascular interactions. In: Remuzzi G, Mecca G, de Gaetano (eds). Haemostasis, prostaglandins, and renal disease. Raven Press New York 1980:175.

- Morin JP, Faroul E, Lamas JP, Leoni J, Lassner J. La prevention des thromboses veineuses profondes par le polysulfate de pentosane. *Cah Anaesthesiol* 1978, 26:297.
- Mühe E. Die Wirkung von elastischen Verbänden auf die venösen Strömungsgeschwindigkeiten in der postoperativen Thromboseprophylaxe. *Krankenhausarzt* 1974, 47:3.
- Mühe E, Burghardt K-H, Kolb W, Strobel G. Eine neue Methode zur Prophylaxe postoperativer Venenthrombosen. *Klinikerzt* 1975, 4:88.
- Müller-Schweinitzer E. In vitro studies on the duration of action of dihydroergotamine. *Int J Clin Pharmacol Ther Tox* 1980, 18:88.
- Negus D, Friedgood A, Cox SJ, Peel ALG, Wells BW. Ultra-low dose intravenous heparin in the prevention of postoperative deep-vein thrombosis. *Lancet* 1980, I:891.
- Negus D, Pinto DJ, Brown N. Platelet adhesiveness in postoperative deep-vein thrombosis. *Lancet* 1969, I:220.
- Nicolaides AN, Fernandes e Fernandes J, Pollock AV. Intermittent sequential pneumatic compression of the legs in the prevention of venous stasis and postoperative deep venous thrombosis. *Surgery* 1980, 87:69.
- Nicolaides AN, Kakkar VV, Field ES, Fish P. Soleal veins, stasis and prevention of deep vein thrombosis. In: Kakkar VV, Jouhar AJ (eds). *Thromboembolism: diagnosis and treatment*. Churchill Livingstone, Edinburgh, London. 1972:69.
- Niewiarowski S. Proteins secreted by the platelet. *Thromb Haemost* 1977, 38:924.
- Nillius A, Nylander G. Deep vein thrombosis after total hip replacement: a clinical and phlebographic study. *Br J Surg* 1979; 66:324.
- Nilsson IM. Biochemical and clinical aspects of factor VIII. In: Saldeen T (ed). *The microembolism syndrome*. Almqvist & Wiksell, Stockholm. 1979.
- Nilsson IM, Holmberg L, Åberg M, Vilhardt H. The release of plasminogen activator and factor VIII after injection of DDAVP in healthy volunteers and in patients with von Willebrand's disease. *Scand J Haematol* 1980, 24:351.
- Nilsson IM, Pandolfi M. Fibrinolytic response of the vascular wall. *Thromb Diath Haemorrh* 1970, Suppl 40:231.
- Nilsson IM, Vilhardt H, Holmberg L, Åstedt B. Association between factor VIII related antigen and plasminogen activator. *Acta Med Scand* 1982, 211:105.

- Olsson S. Platelets and fibrin in the early development of arterial and venous thrombi. Experimental and methodological studies. Thesis. University of Lund, 1974.
- Owen WG. The control of hemostasis. Role of endothelium in the regulation of inhibitory and catabolic pathways. Arch Pathol Lab Med 1982, 106:209.
- Pauschinger P, Matis P, Rieckert H. Die Veränderung der Durchblutung im Bereich der unteren Extremität infolge Inaktivität und ihre Beeinflussungen durch Trasylol. Med Welt 1968, 51:2822.
- Partsch H, Kahn P. Venöse Strömungsbeschleunigung in Bein und Becken durch "Anti-Thrombose-Strümpfe". Klinikarzt 1982, 11:3.
- Pennica D, Holmes WE, Kohr WJ, Harkins RN, Vehar GA, Ward CA, Bennett WF, Yelverton E, Seeburg PH, Heyneker HL, Goeddel DV, Collen D. Cloning and expression of human tissue-type plasminogen activator cDNA in E. coli. Nature 1983, 301:214.
- Pflug E, Foster C, Martin R, Winter P. Limb blood flow. The influence of temperature during halothane-nitrous oxide anesthesia. Arch Surg 1980, 115:616.
- Popov-Cenic S, Schander K, Noe G, Etzel F. Änderungen von Heparinspiegel sowie Gerinnungsparameter während der postoperativen Prophylaxe mit Heparin und Heparin-Dihydroergot (DHE). In: Tscherne H, Deutsch E (eds). Postoperative Thromboembolie-Prophylaxe aus aktueller Sicht. Georg Thieme Verlag, Stuttgart, New York. 1981:111.
- Raberger G, Schwarz M, Benke T, Kraupp O. Die Wirkungen von Dihydroergotamin auf den grossen und kleinen Kreislauf. In: Tscherne H, Deutsch E. Postoperative Thromboembolie-Prophylaxe aus aktueller Sicht. Georg Thieme Verlag, Stuttgart, New York. 1981:70.
- Raberger G, Seitelberger R, Schütz W, Schlappack O, Korencan A. Beeinflussung der Durchblutung des Stoffwechsels unter der Funktion minderperfundierter Myokardareale durch Dihydroergotamin am Hund. In: Fitscha P (ed). Neuester Stand der Dihydroergot-Forschung. Georg Thieme Verlag, Stuttgart, New York. 1983.
- Reickert H. Primäre Therapieziele bei der hypotonen Fehlregulation. Fortschr Med 1971, 89:173.
- Roberts VC, Cotton LT. Failure of low-dose heparin to improve efficacy of peroperative intermittent calf compression in preventing postoperative deep vein thrombosis. Br Med J 1975, 3:458.
- Robertsson B, Pandolfi M, Nilsson IM. Response of local fibrinolytic activity to venous occlusion of arms and legs in healthy volunteers. Acta Chir Scand 1972, 138:437.

- Ryde M, Eriksson H, Tangen O. Studies on the different mechanisms by which heparin and polysulphated xylan (PZ68) inhibit blood coagulation in man. *Thromb Res* 1981, 23:435.
- Sagar S, Nairn D, Stamatkis JD, Maffei FH, Higgins AF, Thomas DP, Kakkar VV. Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total-hip replacement. *Lancet* 1976, I:1151.
- Sallden T. Trends in microvascular research. The microembolism syndrome. *Microvasc Res* 1976, 11:227.
- Salzman E. Measurement of platelet adhesiveness. A simple in vitro technique demonstrating an abnormality in von Willebrand's disease. *J Lab Clin Med* 1963, 62:724.
- Salzman E, Davies G. Prophylaxis of venous thromboembolism. Analysis of cost effectiveness. *Ann Surg* 1980, 191:207.
- Samuelsson B, Borgeat P, Hammarström S, Murphy RC. Leucotriens: A new group of biologically active compounds. In: Samuelsson B, Ramvelli P, Paoletti R (eds). *Advances in prostaglandin and thromboxane research*. Raven Press, New York. 1980, vol. 6:1.
- Sasahara AA, DiSerio FJ. Prophylaxis of postoperative deep vein thrombosis with a dihydroergotamine-heparin combination: a multicenter trial. *Thromb Haemost* 1983, 50:9.
- Sasahara AA, Sharma GVRK, Parisi AF. New developments in the detection and prevention of venous thromboembolism. *Am J Cardiol* 1979, 43:1214.
- Schmid-Schönbein H. Haemorheology and thrombosis. In: van de Loo J, Prentice CRM, Beller FK (eds). *The thromboembolic disorders*. Schattauer Verlag, Stuttgart, New York. 1983:45.
- Schran HF, Bitz DW, DiSerio FJ, Hirsch J. The pharmacokinetics and bioavailability of subcutaneously administered dihydroergotamine, heparin and the dihydroergotamine-heparin combination. *Thromb Res* 1983, 31:51.
- Schwartz SI, Shay H, Beebe H, Rob C. Effect of low molecular weight dextran on venous flow. *Surg* 1964, 55:106.
- Schöndorf T, Hey D. Combined administration of low dose heparin and aspirin as prophylaxis of deep vein thrombosis after hip joint surgery. *Haemostasis* 1976, 5:250.
- Schöndorf T, Weber U. Prevention of deep vein thrombosis in orthopedic surgery with the combination of low-dose heparin plus either dihydroergotamine or dextran. *Scand J Haematol* 1980, 25:Suppl 36:126.
- Semlararo N, Vermylen J. Evidence that washed human platelets possess factor X activator activity. *Br J Haematol* 1977, 36:107.

- Sevitt S. The structure and growth of valve-pocket thrombi in femoral veins. *J Clin Path* 1974, 27:517.
- Sharnoff JC, Kass HH, Mistica BA. A plan of heparinization of the surgical patient to prevent postoperative thromboembolism. *Surg Gynecol Obstet* 1962, 115:75.
- Sigel B, Edelstein A, Savitch L, Hasty J, Felix R. Type of compression for reducing venous stasis. A study of lower extremities during inactive recumbency. *Arch Surg* 1975, 110:171.
- Smith RC, Elton RA, Orr JD, Hart AJL, Graham DF, Fuller GAG, Rundle JSH, Macpherson AIS, Ruckley CV. Dextran and intermittent pneumatic compression in prevention of postoperative deep vein thrombosis: multiunit trial. *Br Med J* 1978, 1:952.
- Spiro M, Roberts VC, Richards JB. Effect of externally applied pressure on femoral vein blood flow. *Br Med J* 1970, 1:719.
- Stamatakis JD, Kakkar VV, Lawrence D, Bentley PG. The origin of thrombi in the lower limb: a venographic study. *Br J Surg* 1978, 65:449.
- Stamatakis JD, Kakkar VV, Sagar S, Lawrence D, Nairn D, Bentley PG. Femoral vein thrombosis and total hip replacement. *Br Med J* 1977, 2:223.
- Stenflo J. A new vitamin K-dependent protein: purification from bovine plasma and preliminary characterization. *J Biol Chem* 1976, 25:355.
- Stewart GJ, Alburger PD. Venous endothelial damage induced by hip replacement in the dogs. *Fed Proc* 1981, 40:332.
- Stewart GJ, Stern HR, Schaub RG. Endothelial alterations, deposition of blood elements and increased accumulation of ¹³¹I-albumin in canine jugular veins following abdominal surgery. *Thromb Res* 1978, 12:555.
- Stewart GJ, Stern HS, Lynch PR, Malmud LS, Schaub RG. Response of canine jugular veins and carotid arteries to hysterectomy: increased permeability and leucocyte adhesion and invasion. *Thromb Res* 1980, 20:473.
- Stevenson M, Rohr P, Davidson A, Byars E, Hopkins G, Tarnay T. Changes in euglobulin lysis following intermittent pneumatic calf compression. *Thromb Haemost* 1977, 38:263.
- Stoll A, Hofmann A. Partialsynthese von Alkaloiden vom Typus des Ergobasins. 6 Mitt. über Mutterkornalkaloide. *Helv chim Acta* 1943, 26:944.
- Strandness DE, Sumner DS. Hemodynamics for surgeons. Grune & Stratton, New York, San Francisco, London. 1975.
- Suzuki K, Stenflo J, Dahlbäck B, Teodorsson B. Inactivation of human coagulation factor V by activated protein C. *J Biol Chem* 1983, 258:1914.

- Svanberg L, Bernstein K, Kullander S, Åstedt B. Effect of dihydroergotamine on coagulation factors and components of the fibrinolytic system. *Acta Obstet Gynaecol Scand* 1980, 59:251.
- Tarnay TJ, Rohr PR, Davidson AG, Stevenson M, Byars EF, Hopkins GR. Pneumatic calf compression, fibrinolysis and the prevention of deep venous thrombosis. *Surgery* 1980, 88:489.
- Thomsen WB, Green J, Lynn Evans I. The effect of some physiological stimuli on fibrinolytic activity in man measured by the heparin fractionation method. *J Clin Pathol* 1964, 17:341.
- Thorén L. Dextran as a plasma volume substitute. *Progr Clin Biol Res* 1978, 19:265.
- Thorgeirsson G, Robertsson AL. The vascular endothelium - pathobiologic significance. *Am J Path* 1978, 93:803.
- Tillberg B. Prophylaxis of postoperative venous thrombosis by combined leg bandaging and oxyphenbutaxone. Clinical and experimental investigations. *Acta Orthop Scand* 1974, Suppl 158.
- Todd AS, Nunn A. Fibrinolytic activity in tissues and thrombi. In: Tissue factors in the homeostasis of the coagulation fibrinolysis systems. *Unione Chimica Medicamenti*, Turin. 1967:57.
- Törngren S. Low dose heparin and compression stockings in the prevention of postoperative deep venous thrombosis. *Br J Surg* 1980, 67:482.
- Törngren S, Brücke P, Haller U, Hartl P, Hutter O, Kettunen K, Koppenhagen K, Lahnborg G, Lahtinen J, Forsskåhl B. A randomized study of a semisynthetic heparin analogue and heparin in prophylaxis of postoperative deep vein thrombosis. *Thromb Haemost* 1983, 50:52.
- Turitto VT, Weiss HJ. Red blood cells: their dual role in thrombus formation. *Science* 1980, 207:541.
- Turitto VT, Baumgartner HR. Platelet surface interactions. In: Coleman RW, Hirsch J, Marder VJ, Salzman EW (eds). *Haemostasis and thrombosis, basic principles and clinical practice*. JB Lippincott Comp, Philadelphia 1982:364.
- Ulrich J, Jessen B, Siggaard-Andersen J. Comparative effects of dihydroergotamine and hydergin on the blood flow, capillary filtration rate and the capacitance vessels in the human calf studied by pléthysmography. *Angiology* 1973, 24:657.
- van Geloven F, Wittebol P, Sixma JJ. Comparison of postoperative coumarin, dextran 40 and subcutaneous heparin in the prevention of postoperative deep vein thrombosis. *Acta Med Scand* 1977, 202:367.
- Verstraete M. A pharmacological approach to the inhibition of platelet adhesion and platelet aggregation. *Haemostasis* 1982, 12:317.

- Vinazzer H. Gerinnungsparameter unter Low-Dose Heparin und Heparin-DHE. In: Tscherne H, Deutsch E (eds). Postoperative Thromboembolic-Prophylaxe aus aktueller Sicht. George Thieme Verlag, Stuttgart, New York. 1981:108.
- Virchow R. Gesammelte Abhandlungen zur wissenschaftlichen Medizin. Von Meidinger Sohn, Frankfurt a.M. 1856.
- Warlow C, Ogston D, Douglas AS. Deep venous thrombosis of the legs after strokes. Part 1. Incidence and predisposing factors. Br Med J 1976, 1:1178.
- Webb P, Fok J, Kakkar VV. Venous thromboembolism in patients undergoing emergency surgery. Br J Surg 1981, 68:807.
- Wessler S. Factors in the initiation of deep venous thrombosis. In: Nicolaides AN (ed). Thromboembolism. Aetiology, advances in prevention and management. MTP, Lancaster. 1975.
- Wiman B, Collen D. On the kinetics of the reaction between human antiplasmin and plasmin. Eur J Biochem 1978, 84:573.
- Yates CJP, Andrews V, Berent A, Dormandy JA. Increase in leg blood-flow in normovolemic haemodilution in intermittent claudication. Lancet 1979, II:166.
- Yett H, Skillman J, Salzman E. The hazards of aspirin plus heparin. N Engl J Med 1978, 298:1092.
- Ygge J. Studies on blood coagulation and fibrinolysis in conditions associated with an increased incidence of thrombosis. Methodological and clinical investigations. Scand J Haematol 1970, Suppl 11.
- Zederfeldt B. The hemodynamic effects of plasma substitutes. Scand J Clin Lab Invest 1965, 17:Suppl 86;93.
- Zimpfer M, Schwarz M, Stanek B, Raberger G. Cardiovascular effects of dihydroergotamine during epidural anaesthesia in dogs. Pharmacology 1981, 23:305.

CENTRAL HAEMODYNAMIC EFFECTS OF DEXTRAN 70, DIHYDROERGOTAMINE AND THEIR COMBINATION

A Study in Dogs

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(Submitted for publication October 7, 1982. Accepted February 14, 1983)

Abstract. In a study in dogs the central haemodynamic effects of dextran 70 and dihydroergotamine, both separate and combined, were evaluated. Dextran 70 gave an increased cardiac output, and peripheral resistance was reduced. The volume of blood flow in the femoral vein increased, pressure recordings being mainly unchanged. Dihydroergotamine caused an increase in the systemic arterial, central venous and pulmonary artery pressure. Cardiac output was unchanged. Total peripheral resistance increased but pulmonary vascular resistance remained unchanged. The combination of dextran 70 and dihydroergotamine gave a rather more pronounced increase in pressure recordings, but the other parameters observed were only moderately affected.

The effects of dextran 70 on central haemodynamics during hypovolaemia and haemodilution are well known, but there are few published reports concerning the effects in a normo-volaemic situation. Since dextran 70 is widely used for prophylactic treatment against postoperative thromboembolism and since some reports have indicated a risk of circulatory overloading, further evaluation of the central haemodynamic effects is desirable.

Dihydroergotamine (DHE) is an ergot alkaloid with α -receptor affinity but also serotonin and dopamine receptor blocking effects. An increase in tone in capacitance vessels leads to reduced blood pooling and increased central blood volume.

Since both dextran and DHE have been found effective against postoperative thromboembolism and since the mechanism of action at least to some extent differs, it seemed important to analyse whether the combination of dextran 70 and DHE might potentiate this prophylactic effect. As both dextran 70 and DHE affect circulation it was necessary to study the effects on central haemodynamics

before a clinical trial could be made to evaluate the effect of the proposed combination in preventing postoperative thromboembolism.

This study was made in order to evaluate the effects on central haemodynamics of dextran 70, DHE, and the two combined.

MATERIAL AND METHOD

Twenty-two mongrel dogs of both sexes, weighing between 16.5 and 28 kg were used. The dogs were anaesthetized with phenobarbital, initially 50 mg/kg and then intermittently in small doses during the experiment. Body temperature was maintained around 37°C and the ambient room temperature was 20°C.

In two experimental models the combined use of dextran 70 and DHE was evaluated (Fig. 1). In the combined therapy experimental models, 9 dogs received a rapid infusion of dextran 70 (0.5 g/kg) after baseline values were achieved and 15 min later DHE was given (0.01 mg/kg). In the other combined therapy experimental model (9 dogs) DHE was given after baseline values were established and 15 min later the dextran 70 infusion was given. The experiment lasted 60 min in all animals and in 9 it was extended to 240 min.

The following parameters were monitored: electrocardiogram, cardiac output, systemic arterial blood pressure, central venous pressure (9 dogs), pressure in the main trunk of the pulmonary artery, left atrial pressure (9 dogs) and volume blood flow in the femoral vein. Haematocrit as well as the concentrations of dextran and DHE were determined.

Systemic arterial blood pressure was recorded continuously through a polyethylene catheter inserted into the aorta from the femoral artery. *Central venous pressure* was determined continuously in half of the experiments via a polyethylene catheter introduced from the femoral vein. *Pressure in the main trunk of the pulmonary artery* was recorded continuously with a three-channel thermodilution catheter (Swan-Ganz Inc., California, USA) or (in 9 dogs) a silicon catheter. The catheters were introduced

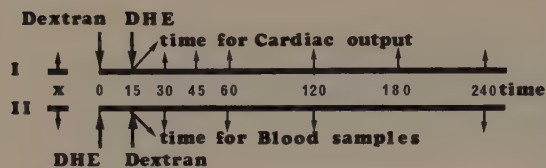


Fig. 1. Time for cardiac output measurements, blood samples and administration of dextran 70 and DHE in experimental models 1 and 2.

either through the femoral or external jugular vein. Under cinéfluoroscopic guidance the catheters were placed in the main trunk of the pulmonary artery. The position was verified by pressure recordings and X-ray examinations after contrast injection.

Pressure in the left atrium was recorded in 9 dogs. A polyethylene catheter was introduced through the right common carotid artery and under cinéfluoroscopic control inserted into the auriculum of the left atrium. This position was verified by pressure recordings and X-ray examination.

Cardiac output was determined using two different techniques—thermodilution (9 dogs) or radioactive microsphere technique (9 dogs).

For thermodilution determinations a three-channel catheter with a thermistor was inserted into the main branch of the pulmonary artery and connected to a cardiac output computer (Edwards, model 9520, Edwards Laboratory, California, USA). For each measurement, 5 ml of glucose (0°C) was given and each determination was the mean of three cardiac output recordings. In the dogs where the radioactive microsphere technique was used the microspheres (15 µm, 3M Company, Minnesota, USA) were labelled with different isotopes in random order and delivered to the left atrium. Approximately three million microspheres were given. Reference organ flow (4.16 ml/min) was taken from a separate polyethylene catheter introduced into the aorta. The radioactivity of samples was measured in a gamma scintillation counter and data were further processed in a computer (Tektronix model 4051, Tektronix Inc., Oregon, USA) according to the MIC-II program (Schosser et al., 1979).

Venous volume blood flow was recorded continuously with an electromagnetic flow recorder (Ether AG, Vienna, Austria). The femoral vein on the side opposite that where the catheters had been introduced was gently exposed and a probe of suitable size placed on the vein and the position fixed.

Total peripheral resistance was calculated from the formula $(MAP - CVP)/Q' = TPR$, where MAP stands for mean arterial blood pressure, CVP for central venous pressure (mmHg) and Q' for cardiac output (ml/sec) and total peripheral resistance (TPR) expressed in resistance units (R units = mmHg sec⁻¹ ml⁻¹). **Pulmonary vascular resistance** was calculated from the formula $PAP - LAP/Q' = PVR$, where PAP stands for mean pulmonary artery pressure, LAP for left atrium pressure (mmHg) and Q' for cardiac output (ml/sec). Pulmonary vascular resistance (PVR) was also expressed in resistance units.

Hematocrit, and concentrations of dextran and DHE

were determined in 9 dogs (Fig. 1). **Dextran concentration** was determined according to the technique of Jenner (1967) (kindly performed by Pharmacia AB, Uppsala, Sweden). **Dihydroergotamine concentration** was determined according to the technique by Rosenthaler & Munzer (1976) (kindly performed by Sandoz AG, Basle, Switzerland).

For further evaluation of the dextran 70 and the DHE effects, a further 4 dogs were investigated. Two dogs received dextran 70 and 2 DHE only. The same haemodynamic parameters were followed and the same methods were used as in the combined experimental models.

Dextran 70 was given in a dose of 0.5 g/kg in a rapid intravenous infusion (1–2 min.) (Macrodex® 6% in NaCl, Pharmacia AB, Uppsala, Sweden). **Dihydroergotamine** was given as dihydroergotamine methansulphonate (Orstanorm®, Sandoz AB, Täby, Sweden) in a dose of 0.01 mg/kg intravenously. All pharmaca were introduced through a separate venous catheter.

Statistics

Statistical calculations were made on a programmable desk computer (Texas SR60, Texas Instruments Inc., Texas, USA) and Student's *t*-test was employed for testing significance between paired observations and the Mann-Whitney rank sum test for unpaired observations. $p < 0.05$ was considered significant.

RESULTS

Hematocrit, concentration of dextran, and DHE values are shown in Table I. Hematocrit was reduced after infusion of dextran 70 ($p < 0.001$) but increased after administration of DHE ($p < 0.001$).

Data from the two combined therapy experimen-

Table I. Hematocrit, concentration of dextran, and dihydroergotamine (mean ± SE)

Minutes	Hematocrit (%)	Dextran (g/l)	DHE (ng/ml)
<i>Results of experimental model 1</i>			
Baseline value	38±1	0	0
15	32±1***	7.17±0.18	0
30	35±1	8.87±1.10	2.11±0.29
60	36±1	6.53±0.12	0.74±0.10
120	36±1	5.90±0.24	0.36±0.06
240	36±1	5.37±0.06	0.23±0.02
<i>Results of experimental model 2</i>			
Baseline value	31±2	0	0
15	35±2***	0	2.38±0.25
30	30±2	6.94±0.66	1.19±0.09
60	31±2	6.57±0.45	0.74±0.08
120	32±2	5.96±0.27	0.42±0.06
240	31±2	5.31±0.11	0.26±0.03

*** $p < 0.001$.

Table II. Total peripheral and pulmonary vascular resistance (TPR and PVR)

R units mmHg sec⁻¹ml⁻¹ (mean ± SE)

Time (min)	Experimental model 1		Experimental model 2	
	TPR	PVR	TPR	PVR
Baseline value	3.31±0.37	0.26±0.10	4.17±0.42	0.20±0.07
15	2.39±0.10***	0.21±0.05*	5.31±1.20**	0.25±0.14
30	3.99±0.38	0.33±0.13	4.14±0.49	0.36±0.14
60	3.62±0.43	0.34±0.12	4.43±0.92	0.46±0.17

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

tal models are presented separately. The baseline values did not differ significantly between these models. Electrocardiograph values were unchanged.

Combined therapy, experimental model one

Rapid infusion of dextran 70 led to increased cardiac output ($p<0.01$, Fig. 2) and since heart rate was unaffected (baseline value 134 ± 6 , 15 min after dextran 70 infusion 129 ± 8), stroke volume increased (Fig. 2). Systemic arterial and central venous pressure were unaltered (Fig. 3). Pressure in the main trunk of the pulmonary artery rose from 11.2 to 14.2 mmHg 15 min after the administration of dextran 70 ($p<0.05$); corresponding values for left atrium pressure were 4.5 and 11.5 mmHg. Both total peripheral and pulmonary vascular resistance were significantly reduced by dextran 70 (Table II). The volume blood flow in the femoral vein was increased significantly ($p<0.001$, Table III).

Fifteen minutes after the rapid dextran infusion, DHE was given. Cardiac output decreased to base-

line values (Fig. 2) but since heart rate was reduced (baseline value 134 ± 6 , 15 min after adding DHE 111 ± 10 , $p<0.05$), stroke volume was unaffected (Fig. 2). Addition of DHE gave a rise in systemic arterial blood pressure ($p<0.001$, Fig. 3) and central venous pressure ($p<0.01$). Pulmonary artery pressure increased further from 14.2 to 22.8 mmHg 5 minutes after DHE was administered ($p<0.001$). Left atrium pressure showed a corresponding increase (14.5 mmHg). Total peripheral (but not pulmonary) vascular resistance increased after addition of DHE (Table II). The volume blood flow was unchanged (Table III). In eight of the nine experiments, a sharp rise in volume blood flow in the femoral vein was recorded immediately after DHE injection, lasting for about a minute, followed by a slight reduction in blood flow. This is illustrated in Fig. 4.

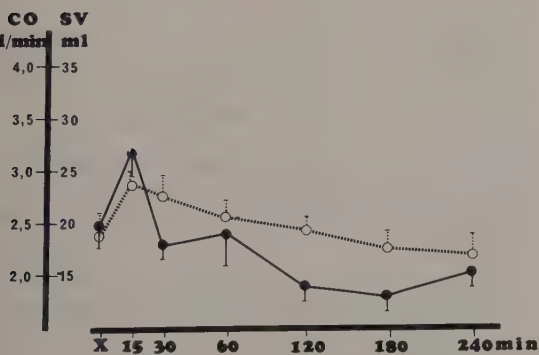


Fig. 2. Cardiac output (●) and stroke volume (○) in experimental model 1 (mean values ± SE).

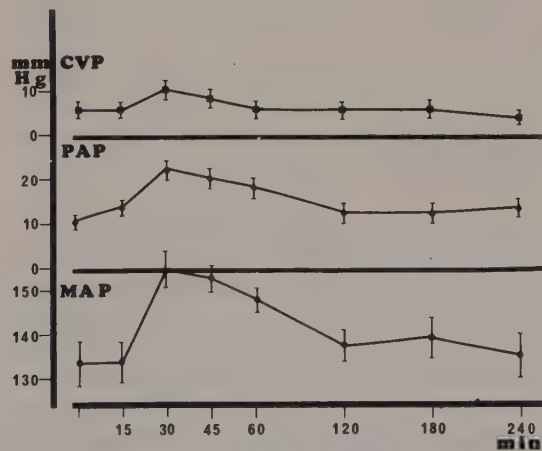


Fig. 3. Pressure recordings in experimental model 1 (mean values ± SE).

Table III. Volume blood flow in the femoral vein (ml/min), (mean ± SE)

Time (min)	Experimental model 1	Experimental model 2
Baseline value	73±14	80±10
5	110±17***	79±12
15	119±17**	75±12
20	105±15*	84±14
30	95±14	89±15
60	82±14	83±14
120	90±18	100±17
180	82±21	97±17
240	73±17	96±18

* $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Combined therapy, experimental model two

After DHE administration, cardiac output was unchanged (Fig. 5) but since heart rate was reduced (baseline value 125 ± 5 , 15 min after DHE 107 ± 5 , $p<0.001$) stroke volume increased, though non-significantly (Fig. 5). Arterial blood pressure rose ($p<0.05$); central venous pressure and pressure in the left atrium also rose (Fig. 6). Pulmonary artery pressure rose from a baseline value of 4.5 mmHg to a maximum of 15.4 mmHg 5 min after DHE was administered ($p<0.01$). Left atrium pressure rose from 4.5 to 13 mmHg 15 min after DHE. The volume blood flow in the femoral vein was unchanged (Table III). No sharp rise was seen after DHE administration. Total peripheral resistance increased ($p<0.01$, Table II), but pulmonary vascular resistance was unchanged.

In experimental model two, the dextran infusion was given 15 min after the administration of DHE. A slight but insignificant rise in cardiac output was

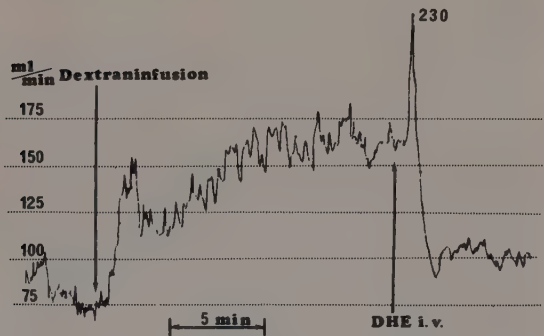


Fig. 4. Volume blood flow changes in the femoral vein (expt no. 10) by dextran infusion and DHE administration.

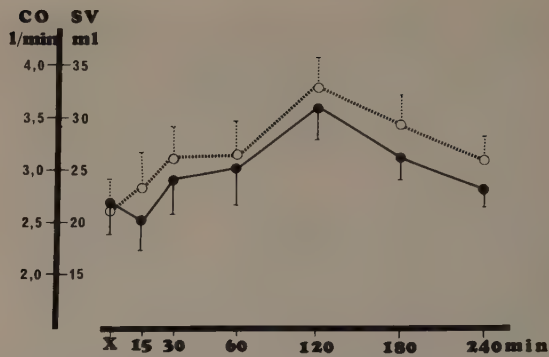


Fig. 5. Cardiac output (●) and stroke volume (○) in experimental model 2 (mean values ± SE).

recorded (Fig. 5). Heart rate was unchanged and no further increase in systemic arterial blood pressure was seen after addition of dextran 70. Pressure recordings from central veins, main trunk of pulmonary artery and the left atrium showed a slight but non-significant further increase. The volume blood flow increased significantly when the values just before and 15 min after infusions of dextran were compared ($p<0.05$, Table III).

In the four investigations where dextran 70 and DHE were administered separately, the results correlate well to the findings from the combined experimental models.

Dextran 70 increased cardiac output (23%, 15 min after infusion) heart rate, pressure recordings being unchanged. DHE reduced cardiac output (15%, 15 min after DHE administration), heart rate also being reduced (19%). Systemic arterial pres-

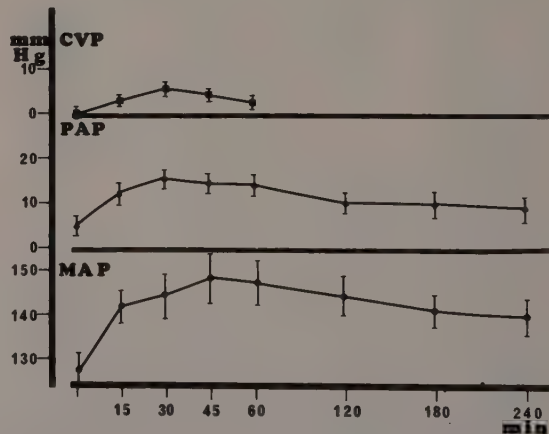


Fig. 6. Pressure recordings in experimental model 2 (mean values ± SE).

sure increased (8%) as did pulmonary artery pressure (19%). The alterations generally returned to normal within 60 min.

DISCUSSION

Dextran 70 is used for plasma volume expansion (Thorén, 1978) and for prophylaxis against postoperative thromboembolism (Bergentz, 1978). Both central and peripheral blood flow are affected by dextran and a general increase in tissue blood flow is noted. The blood flow promoting effect peripherally depends mainly on haemodilution (Gruber & Messmer, 1977). Central haemodynamics are altered mainly due to increased plasma volume and the risk of developing a circulatory overload, especially in elderly patients, is well known.

Dihydroergotamine increases the tonus in vessels, especially in capacitance vessels (Mellander & Nordenfelt, 1970). Blood pooling is reduced and central blood volume increases (Mostbeck & Partsch, 1978). Blood flow velocity in the veins increases (Mühe et al., 1975). DHE is used to prevent hypotension during nerve block (Bergenwald et al., 1972; Castenfors et al., 1975) but has also been shown to have a prophylactic effect on postoperative thromboembolism (Buttermann et al., 1975).

The study was divided into experimental models allowing evaluation of the effect of dextran 70 and DHE separately, and in combination. The dextran infusion was made very rapidly, which gives a maximal volume load that could interact with some of our findings.

The reliability of measuring cardiac output by radioactive microspheres is good and correlation to other methods is high (Archie et al., 1973; Tsuchiya et al., 1978; Segdal & Svanes, 1979; Ishise et al., 1980) also to thermodilution (Arvidsson et al., in press). Because of this good correlation the results of the thermodilution and microspheric methods were interpreted together.

Earlier studies have shown that dextran 70 expands the plasma volume by haemodilution and increases cardiac output without major alterations in pressure recordings (Stetz et al., 1969; Lamke & Liljedahl, 1976). The increased volume blood flow recorded is consistent with the flow-promoting effect of dextran 70, due not only to increased plasma volume but also to the haemodilution, which reduces viscosity (Gelin & Thorén, 1961). Total pre-

peripheral resistance was reduced by the administration of dextran 70.

Dihydroergotamine increased hematocrit. One explanation could be that the dogs were not splenectomized, another that capillary permeability is affected, thus reducing plasma volume. In a pharmacokinetic investigation, dextran concentrations increased when DHE was added (Lindblad et al., in press). In plethysmographic studies, however, no effect on CFR has been found (Mellander & Nordenfelt, 1970).

Cardiac output was unchanged by DHE, but since heart rate was reduced, stroke volume increased. This is in agreement with findings in dogs (Schwarz & Kraupp, 1979) and in man (Harris et al., 1963; Reichelt et al., 1980*b*). The increased pressure in the pulmonary artery also seen in both dog and man (Harris et al., 1963; Schwarz & Kraupp, 1979) seems to be due mainly to an increase in wedge pressure, pulmonary vascular resistance being unchanged. Left atrial pressure rose from 4.5 (baseline level) to 13 mmHg 15 min after DHE was given. Systemic arterial blood pressure was increased by DHE, as has been shown by several others in both dog and man (Halmágyi et al., 1953; Harris et al., 1963; Bevegård et al., 1974; Schwarz & Kraupp, 1979; Reichelt et al., 1980*a, b*). Total peripheral resistance increased. DHE thus caused an increased after-load on the heart despite the increased central blood volume. A constriction of the vascular bed in the systemic (but not in the pulmonary) circulation was achieved by DHE; this is in agreement with the findings by Schwarz & Kraupp (1979) and Reichelt et al. (1980*b*).

Volume blood flow was mainly unchanged by DHE, but a brief, sharp increase was seen in the dogs that had received dextran, having a rather high volume blood flow (Fig. 4). This short-lasting increase could be due to the increased tonus in capacitance vessels and reduced blood pooling achieved by DHE.

Aellig (1967) has proposed that peripheral blood flow is reduced or increased following administration of DHE, due to pre-existing tonus in resistance vessels. This could not be verified in our study. Boismare et al. (1975) and Castenfors et al. (1975) have shown that when volume blood flow is low, DHE causes an increase. When the flow is high, DHE causes a reduction in blood flow. This corresponds to our results and supports the opinion that the α -receptor blocking agent, DHE, exerts differ-

ent effects on volume blood flow in the leg, depending on the existing sympathetic tonus at administration.

The effects of dextran 70 differed, depending on whether the vascular bed was affected by DHE or not. If the vascular bed had been treated with DHE only a slight increase in cardiac output and venous volume blood flow was seen. The α -receptor blocking activity of DHE seems to reduce the effect of the volume increase.

The combination of dextran 70 and DHE showed in our study somewhat more pronounced pressure effects but they were normalized to baseline conditions within 90 min. It is known that DHE increases central blood volume (Mostbeck & Partsch, 1978; Koppenhagen et al., 1979; Reichelt et al., 1980a) and that dextran 70 by hemodilution increases plasma volume (Gruber & Messmer, 1977). In spite of these effects the alterations in central haemodynamics were modest. Wyatt et al. (1977) have shown that an increased pre-load can reduce coronary blood flow, but this does not occur when an increased after-load is also present. This increased after-load is achieved by DHE. Despite an increased central blood volume and plasma volume expansion, the central haemodynamic effect of the combination of dextran 70 and DHE was moderate and tolerable. The effects seen on central haemodynamics in this study permit further evaluation of the proposed combination of dextran 70 and dihydroergotamine for thromboembolic prophylaxis.

ACKNOWLEDGEMENTS

The skilful technical assistance of Gunnel Fredrickson and Inger Nilsson is greatly appreciated. This study was supported by grants from Pharmacia AB, Uppsala, Sweden, Sandoz AB, Täby, Sweden, the Swedish Medical Research Council (B81-17X-00759-15A) and University of Lund, Sweden.

REFERENCES

- Aellig, W. H. 1967. Periphere Kreislaufwirkungen von Ergotamin, Dihydroergotamine und 1-Methyl-ergotamin an der innervierten, perfundierten Hinterextremität des Hundes. *Helv Physio Pharmacol Acta* 25, 374.
- Archie J. P., Fixler, D., Ulliyot, D., Hoffman, J., Uttey, J. & Carlson, E. 1973. Measurement of cardiac output with and organ trapping of radioactive microspheres. *J Appl Phys* 35, 148.
- Arvidsson, S., Bergqvist, D., Haglund, U. & Lindblad, B. 1983. Cardiac output measurements with thermodilution and radioactive microspheres. A comparative study in cats. [In press].
- Bergentz, S.-E. 1978. Dextran in the prophylaxis of pulmonary embolism. *World J Surg* 2, 19.
- Bergenswald, L., Eklund, B., Kaijser, L. & Klingenström, P. 1972. Hemodynamic effects of dihydroergotamine during spinal anaesthesia in man. *Acta Anaesthesiol Scand* 16, 235.
- Bevegård, S., Castenfors, J. & Lindblad, L. E. 1974. Hemodynamic effects of dihydroergotamine in patients with postural hypotension. *Acta Med Scand* 196, 473.
- Boismare, F., Hacpille, L., Belliard, J.-P. & Colin, C. 1975. Influence de la dihydroergotamine sur l'hypotension posturale induite, chez le chien, par la lévomépromazine. *J Pharmacol (Paris)* 6, 391.
- Buttermann, G., Theisinger, W., Oechsler, H. & Hör, G. 1975. Untersuchungen über die postoperativen Thromboemboli-Pharylaxe nach einem neuen medikamentösen Behandlungsprinzip. *Dtsch Med Wschr* 41, 2065.
- Castenfors, J., Lindblad, L. E. & Mortasawi, A. 1975. Effect of dihydroergotamine on peripheral circulation during epidural anaesthesia in man. *Acta Anaesth Scand* 19, 79.
- Gelin, L.-E. & Thorén, O. 1961. Influence of low viscous dextran on peripheral circulation in man. *Acta Chir Scand* 122, 303.
- Gruber, U. F. & Messmer, K. 1977. Colloids for blood volume support. *Progr Surg* 15, 49.
- Halmágyi, D., Iványi, J., Felkai, B., Zsótér, T., Tényi, M. & Szűcs, J. 1953. The effect of dihydroergotamine and hydergine on pulmonary arterial pressure in man. *Scand J Clin Lab Invest* 5, 85.
- Harris, P., Bishop, J. M. & Segel, N. 1963. The effects of dihydroergotamine tartrate on the pulmonary and systemic circulation in man. *Clin Sci Molec Med* 25, 443.
- Ishise, S., Pegram, B., Yamamoto, J., Kitamura, Y. & Frohlich, E. 1980. Reference sample microsphere method: cardiac output and blood flows in conscious rat. *Am J Physiol* 239, 443.
- Jenner, H. 1967. Automated determination of the molecular weight distribution of dextran. *Europ Technicon Symp*, Brighton, England, p. 203.
- Koppenhagen, K., Vogt, L. & Wenig, H. C. 1979. Dihydroergotamin-Wirkung auf die Lungenperfusion im Akzelerationsstress. *Dtsch Med Wschr* 104, 1208.
- Lamke, L.-O. & Liljedahl, S.-O. 1976. Plasma volume changes after infusion of various plasma expanders. *Resuscitation* 5, 93.
- Lindblad, B., Abisch, E. & Bergqvist, D. 1983. Pharmacokinetics of subcutaneous dihydroergotamine with and without dextran infusion. *Group J Clin Pharmacol*. In press.
- Mellander, S. & Nordenfelt, I. 1970. Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. *Clin Sci* 39, 183.
- Mostbeck, A. & Partsch, H. 1978. Umverteilung regionaler Blutvolumina durch Dihydroergotamin und Beinkompression. *Med Klin* 73, 801.
- Mühe, E., Burghardt, K.-H., Kolb, W. & Strobel, G. 1975. Eine neue Methode zur Prophylaxe postoperativer Venenthrombosen. *Klinik Arzt* 4, 88.
- Reichelt, W., Piepenbrock, S., Schleussner, E. & Steg-

- mann, T. 1980 *a*. Die Wirkungen von Dihydroergotamin auf Volumengehalt und Compliance der extrathorakalen Kapazitätsgefäße des Menschen unter Narkosbedingungen während extrakorporaler Zirkulation in Hypothermie. *Z Kardiol* 69, 67.
- Reichelt, W., Piepenbrock, S., Schleussner, E., Stegmann, T. & Hempelmann, G. 1980 *b*. Die Wirkungen von Dihydroergotamin auf Herz und Kreislauf des Menschen unter Neuroleptanalgesie. *Anaesthesist* (Berlin) 29, 429.
- Rosenthaler, J. & Munzer, H. 1976. 9, 10-Dihydroergotamine: Production of Antibodies and Radioimmunoassay. *Experientia* (Basel) 32, 234.
- Schossner, R., Arfors, K.-E. & Messmer, K. 1979. MIC-II: A program for the determination of cardiac output, arterio-venous shunt and regional blood flow using the radioactive microsphere method. *Comp Progr Biomedicine* 9, 19.
- Schwarz, M. & Kraupp, O. 1979. Effects of dihydroergotamine (DHE) on pulmonary and systemic circulation. *Naunyn-Schmiedeberg's Arch Pharmacol* 308, Suppl. P. R. 18.
- Segdal, L. & Svanes, K. 1979. Evaluation of the microsphere-method for determination of cardiac output. *Scand J Clin Lab Invest* 39, 415.
- Stetz, J. J., Jelinek, G. N., Wolfman, M., Autell, H., Fries, C. C. & Stuckley, J. H. 1969. Blood flow in the intact extremity. A comparison of the effect of intravenous administration of glucose and dextran 40. *Arch Surg* 99, 589.
- Thorén, L. 1978. Dextran as a plasma volume substitute. *Progr Clin Biol Res* 19, 265.
- Tsuchiya, M., Ferrone, R., Walsh, G. & Frohlich, E. 1978. Regional blood flows measured in conscious rats by combined Fick and microsphere methods. *Am J Physiol* 235, H 357.
- Wyatt, H. L., Protasio, L. Da Lux., Waters, D., Swan, H. J. C. & Forrester, J. 1977. Contrasting influences of alterations in ventricular preload and afterload upon systemic haemodynamics, function and metabolism of ischemic myocardium. *Circulation* 55, 318.

TISSUE BLOOD FLOW AND BLOOD FLOW DISTRIBUTION AFTER ADMINISTRATION OF DEXTRAN 70, DIHYDROERGOTAMINE AND THEIR COMBINATION

A Study in Dogs Using the Radioactive Microsphere Technique

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(Submitted for publication October 7, 1982. Accepted February 14, 1983)

Abstract. The radioactive microsphere technique was used to measure tissue blood flow after administration of dextran 70 and dihydroergotamine, both separate and in combination, in normovolemic dogs. Dextran 70 increased cardiac output and tissue blood flow to most organs. Unchanged blood flow after dextran 70 to CNS, liver (hepatic artery blood flow), adrenals, genitals, uterus and lungs (bronchial artery and arteriovenous shunts) was found. Dihydroergotamine administration did not alter cardiac output. Tissue blood flow to pancreas and thyroid was reduced and CNS-tissue blood flow increased. Heart tissue blood flow was unaffected. When dihydroergotamine was given after dextran 70 had been infused, tissue blood flow returned to baseline values—except for pancreas and thyroid, where tissue blood flow was reduced, and CNS-tissue, where blood flow was increased. When dextran 70 was infused after dihydroergotamine, cardiac output and tissue blood flow remained mainly unchanged.

Dextran 70 is an effective prophylactic substance against postoperative thromboembolism. Its effects on lysisability and structure of thrombi, platelet function and factor VIII have been elucidated by Åberg (1978). The effects on tissue blood flow and blood flow distribution in a normovolemic situation have not been fully established.

Dihydroergotamine (DHE) is an ergot alkaloid with α -receptor affinity and serotonin and dopamine receptor blocking effect. Tonus in capacitance vessels increases, thereby reducing peripheral blood pooling (Mellander & Nordenfelt, 1970), while central blood volume is increased (Mostbeck & Partsch, 1978). A more widespread use of DHE is seen both for the prevention of hypotension during spinal or epidural nerve blockade (Bergenswald et al., 1972; Castenfors et al., 1975) and for prophylaxis against postoperative thromboembolism (Buttermann et al., 1975), usually in combination with

low-dose heparin (Sagar et al., 1976; Bergqvist et al., 1980).

Dextran 70 and DHE are effective in reducing postoperative thromboembolism. They have to some extent differing modes of action, which is why it seems important to evaluate the effectiveness of their combination in preventing thromboembolism. Before a clinical study can be made it is essential to evaluate the haemodynamic effects as well as changes in blood flow distribution and tissue blood flow of such a combination.

The aim of this study was to investigate changes in tissue blood flow and blood flow distribution following administration of dextran 70 and DHE, both separately and in combination. The study made use of the radioactive microsphere technique for flow determinations.

MATERIAL AND METHODS

Nine dogs of both sexes weighing between 16.5 and 26.5 kg were used. The dogs were anaesthetized intravenously with phenobarbital, initially 50 mg/kg, then with intermittent maintenance doses. At the end of experiment the dogs were sacrificed with an overdose of phenobarbital.

The body temperature of the dogs was maintained at around 37°C and the ambient room temperature at 20°C.

Two experimental models were studied: in the first, dextran 70 was given and 15 min later DHE; in the other, the substances were given in the reverse order.

The following hemodynamic parameters were observed during the experiments: cardiac output, systemic arterial pressure, central venous pressure, pressure in the main trunk of the pulmonary artery, pressure in the left atrium, volume blood flow in the femoral vein, and electrocardiographic recordings. For details in methodology and results, see Lindblad & Bergqvist (1983). Through the right common carotid artery a polyethylene catheter was intro-

Table I. Tissue blood flow in experimental model 1 (mean $\pm$ SE)TBF=tissue blood flow (ml min⁻¹ 100 g⁻¹)

Organ	Baseline values	15 min after dextran 70	15 min after adding DHE	At end of expt
Body muscle	6 $\pm$ 1	9 $\pm$ 1***	5 $\pm$ 1	5 $\pm$ 1
Stomach	24 $\pm$ 7	39 $\pm$ 5**	49 $\pm$ 20	40 $\pm$ 11
Small intestine	78 $\pm$ 8	107 $\pm$ 14*	73 $\pm$ 11	78 $\pm$ 17
Large intestine	60 $\pm$ 20	98 $\pm$ 30***	56 $\pm$ 15	51 $\pm$ 17
Spleen	90 $\pm$ 7	117 $\pm$ 12*	108 $\pm$ 11	128 $\pm$ 23
Hepar	16 $\pm$ 4	21 $\pm$ 5	15 $\pm$ 4	30 $\pm$ 12
Pancreas	36 $\pm$ 8	49 $\pm$ 11*	27 $\pm$ 4	24 $\pm$ 5
Adrenals	226 $\pm$ 59	218 $\pm$ 47	176 $\pm$ 30	194 $\pm$ 32
Kidneys	272 $\pm$ 42	305 $\pm$ 42***	278 $\pm$ 30	352 $\pm$ 44***
Testis/ovaries	26 $\pm$ 7	30 $\pm$ 6	27 $\pm$ 7	25 $\pm$ 5
Uterus	18 $\pm$ 5	36 $\pm$ 9*	55 $\pm$ 8*	36 $\pm$ 11
Lungs	57 $\pm$ 10	58 $\pm$ 12	69 $\pm$ 11	50 $\pm$ 8
Heart	90 $\pm$ 28	130 $\pm$ 12	99 $\pm$ 16*	124 $\pm$ 16**
Thyroid	221 $\pm$ 48	218 $\pm$ 32	159 $\pm$ 23*	187 $\pm$ 25
CNS	38 $\pm$ 3	40 $\pm$ 2	58 $\pm$ 10***	51 $\pm$ 5***

Significance correlated to baseline values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

duced and under cinéfluoroscopic guidance and pressure recordings, advanced into the left atrium.

Regional blood flow was determined by using the radioactive microsphere technique. The principles and validity of this technique were described in detail by Heymann et al. (1977). A suspension of approximately three million microspheres (diameter 15 μ m, 3M Tracer Microspheres, 3M Company, St Paul, Minn., USA) labelled with ⁵⁷Co, ⁸⁵Sr, ⁹⁵Nb or ⁶⁵Zn in 10% dextran containing 0.05% of Tween 80 was vigorously shaken by a mechanical shaker and then immediately injected into the left atrium. The injection took 30–60 sec. Reference organ flow was led from the aorta through a separate polyethylene catheter at a rate of 4.16 ml/min and collected 10 sec before, during, and 60 sec after the injection of the labelled microspheres. The isotopes were given in random order and during the experiment four determinations of tissue blood flow were made.

At the end of the experiment the dogs were sacrificed and 53 tissue specimens (about 1–2 g each) from each dog were removed and weighed. Their radioactivity was measured in an automatic gamma-scintillation counter (Packard Model 5986, Packard Instrument Company, Inc., Downers Grove, Ill., USA) equipped with a multi-channel analyser and using suitable windows for optimal discrimination of the isotopes used. The total injected radioactivity was calculated as the difference in counts of the special microsphere syringe connecting catheters and stopcock that was used, before and after each injection. The number of injected microspheres (approx. 3 million) was calculated from the activity of a known number of radiolabelled microspheres and correlated to the total injected radioactivity.

The data were processed by a Tektronix computer (Model 4051, Tektronix Inc., Beaverton, USA) according to the MIC-II program (Schosser et al., 1979). This program gave data on cardiac output (l/min), tissue blood

flow (ml min⁻¹ 100 g⁻¹) and blood flow as percentages of cardiac output.

The calculated values for tissue blood flow in each dog are the mean values for at least two specimens analysed, but for skeletal muscle ten, heart ten, central nervous system eight and lungs four specimens were analysed.

The aim of the study was to evaluate the effects of dextran 70 and DHE, both separate and combined and the experiments were therefore divided into two parts. After baseline values had been established, for tissue blood flow, the first 5 dogs received a rapid infusion (1–2 min) of dextran 70 (Macrodex® 6% in NaCl, Pharmacia AB, Uppsala, Sweden) in a dose of 0.5 g/kg (8.33 ml/kg). Fifteen minutes later dihydroergotamine methanesulphonate (Orstanorm®, Sandoz AB, Täby, Sweden) was given intravenously in a dose of 0.01 mg/kg. In the last 4 dogs, DHE was given after baseline values was obtained and 15 min later dextran 70 was given. Tissue blood flow was

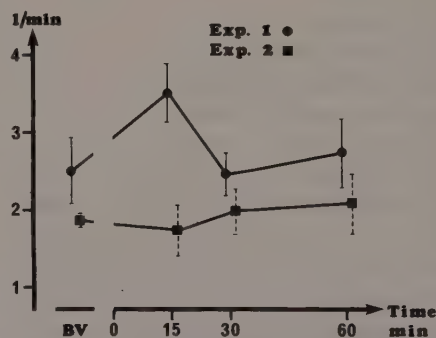


Fig. 1. Cardiac output under baseline conditions and during experiments (mean $\pm$ SE).

Table II. Tissue blood flow in experimental model 2 (mean value $\pm$ SE)TBF=tissue blood flow (ml min⁻¹ 100 g⁻¹)

Organ	Baseline values	15 min after DHE	15 min after adding dextran 70	At end of expt
Body muscle	3 $\pm$ 1	3 $\pm$ 1	3 $\pm$ 1	3 $\pm$ 1
Stomach	25 $\pm$ 4	18 $\pm$ 3	20 $\pm$ 4	26 $\pm$ 6
Small intestine	75 $\pm$ 14	65 $\pm$ 10	77 $\pm$ 17	71 $\pm$ 12
Large intestine	77 $\pm$ 14	65 $\pm$ 18	87 $\pm$ 14	69 $\pm$ 14
Spleen	105 $\pm$ 41	92 $\pm$ 15	116 $\pm$ 23	133 $\pm$ 34
Hepar	13 $\pm$ 5	8 $\pm$ 4	7 $\pm$ 3	10 $\pm$ 4
Pancreas	44 $\pm$ 5	30 $\pm$ 4*	42 $\pm$ 6	37 $\pm$ 7
Adrenals	167 $\pm$ 8	161 $\pm$ 19	156 $\pm$ 12	156 $\pm$ 21
Kidneys	246 $\pm$ 20	220 $\pm$ 23	246 $\pm$ 24	267 $\pm$ 27
Testis/ovaries	19 $\pm$ 3	21 $\pm$ 7	20 $\pm$ 4	17 $\pm$ 3
Uterus	11 $\pm$ 1	9 $\pm$ 1	14 $\pm$ 2	17 $\pm$ 4
Lungs	105 $\pm$ 38	176 $\pm$ 82	141 $\pm$ 48	140 $\pm$ 62
Heart	118 $\pm$ 32	120 $\pm$ 31	138 $\pm$ 26	128 $\pm$ 29
Thyroid	154 $\pm$ 33	130 $\pm$ 36*	121 $\pm$ 47	139 $\pm$ 49
CNS	65 $\pm$ 8	108 $\pm$ 27***	88 $\pm$ 14**	77 $\pm$ 17*

Significance correlated to baseline values: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

determined as baseline values and 15 min after administration of each substance and also at the conclusion of the experiments.

The data of this study were further processed in a programmable desk computer (Texas SR60, Texas Instruments Inc., Houston, USA) giving mean values and standard deviations. Statistical analysis was made as paired samples according to Student's *t*-test. The level of significance chosen was $p<0.05$.

RESULTS

Infusion of dextran 70 significantly ($p<0.05$) increased cardiac output, which was mainly unaffected by DHE (Fig. 1). After plasma volume expansion with dextran 70, DHE gave a reduction in cardiac output to control levels, but when plasma volume expansion was done after DHE administration, cardiac output did not change. Pressure re-

cordings were mainly unchanged after infusion of dextran 70. DHE gave a slight increase in central venous pressure and a more pronounced increase in systemic arterial blood pressure and pressure in the main trunk of the pulmonary artery. DHE gave, in contrast to dextran 70, a reduction in heart rate (for details see Lindblad & Bergqvist, 1983). No pathological electrocardiographic findings were seen after administration of the substances or injection of microspheres.

In Table I, tissue blood flow values are given for experimental model I (dextran 70 before DHE). After dextran 70 infusion an increase in cardiac output and a proportional increase in tissue blood flow was found, except for the liver (hepatic artery blood flow), adrenals, kidneys, genitals, uterus, lungs (bronchial artery blood flow and blood flow through arterio-venous shunts), thyroid and central

Table III. Tissue blood flow in different parts of the heart

Results in experimental model 1 (ml min⁻¹ 100 g⁻¹), (mean value $\pm$ SE)

Part	Baseline values	15 min after dextran 70	15 min after DHE	At end of expt
Left ventricle	130 $\pm$ 19	186 $\pm$ 10***	163 $\pm$ 11**	158 $\pm$ 17*
Septum	140 $\pm$ 19	192 $\pm$ 13***	190 $\pm$ 23	178 $\pm$ 14
Right ventricle	60 $\pm$ 11	85 $\pm$ 12***	83 $\pm$ 14***	82 $\pm$ 14***
Left atrium	60 $\pm$ 11	93 $\pm$ 19*	131 $\pm$ 33*	126 $\pm$ 29*
Right atrium	20 $\pm$ 3	38 $\pm$ 7**	46 $\pm$ 8*	41 $\pm$ 7*

Significance correlated to baseline values: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Table IV. *Tissue blood flow in different parts of the heart*Results in experimental model 2 ($\text{ml min}^{-1} 100 \text{ g}^{-1}$), (mean value $\pm$ SE)

Part	Baseline values	15 min after DHE	15 min after dextran 70	At end of expt
Left ventricula	165 $\pm$ 42	173 $\pm$ 39	172 $\pm$ 15	162 $\pm$ 24
Septum	183 $\pm$ 42	167 $\pm$ 39	185 $\pm$ 23	159 $\pm$ 21
Right ventricula	72 $\pm$ 19	88 $\pm$ 32	91 $\pm$ 15	98 $\pm$ 19
Left atrium	62 $\pm$ 25	66 $\pm$ 26	81 $\pm$ 30	74 $\pm$ 32
Right atrium	54 $\pm$ 22	53 $\pm$ 11	126 $\pm$ 57	111 $\pm$ 54

nervous system, where it was unchanged. After addition of DHE, tissue blood flow values returned to baseline, and a further reduction of tissue blood flow to pancreas and thyroid was noted. The tissue blood flow increased to uterus and the central nervous system (Table I).

Tissue blood flow to all parts of the heart increased significantly, but blood flow distribution was unchanged after administration of dextran 70 (Table III). A slight but variable reduction was seen after addition of DHE, but fractioned blood flow distribution as a percentage of cardiac output increased from 3.7% to 5.4%. Blood flow to all parts of the central nervous system was unaffected by dextran 70 infusion (Table V).

The tissue blood flow results in experimental model (DHE before dextran 70) are presented in Table II. DHE gave a significant reduction of tissue blood flow to pancreas and thyroid, whereas other endocrine organs did not show any alterations. After adding dextran 70, tissue blood flow was unchanged.

Tissue blood flow to the heart was unaffected by

the administration of DHE (Table IV). Adding dextran 70 did not alter heart tissue blood flow either.

In both experimental models an increase in blood flow to all parts of the central nervous system was noted when DHE was given (Tables V and VI). Both white and grey substance of cerebrum and cerebellum showed significantly increased flow.

DISCUSSION

For measurement of blood flow to several organs and for determinations of blood flow distribution the radioactive microsphere technique is suitable and reliable and its use is well established in dogs (Rudolph & Heymann, 1967; Domenech et al., 1969; Heymann et al., 1977).

There are no investigations on tissue blood flow using the radioactive microsphere technique after administration of dextran 70 under normovolemic conditions nor after administration of DHE. The aim of this investigation was to evaluate the alterations in tissue blood flow caused by dextran 70, DHE, and the two combined.

Table V. *Tissue blood flow in different parts of the central nervous system*Results in experimental model 1 ($\text{ml min}^{-1} 100 \text{ g}^{-1}$), (mean value $\pm$ SE)

Part	Baseline values	15 min after dextran 70	15 min after DHE	At end of expt
Cerebrum				
grey tissue	43 $\pm$ 4	44 $\pm$ 3	68 $\pm$ 17***	61 $\pm$ 18***
white tissue	34 $\pm$ 2	35 $\pm$ 1	49 $\pm$ 4***	45 $\pm$ 4*
Cerebellum				
grey tissue	45 $\pm$ 1	48 $\pm$ 4	71 $\pm$ 11**	57 $\pm$ 7*
white tissue	46 $\pm$ 2	50 $\pm$ 3	66 $\pm$ 5***	56 $\pm$ 4
Thalamus	35 $\pm$ 1	35 $\pm$ 2	54 $\pm$ 5*	47 $\pm$ 4**
Medulla	32 $\pm$ 2	33 $\pm$ 3	52 $\pm$ 5*	41 $\pm$ 2

Significance correlated to baseline values: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table VI. Tissue blood flow in different parts of the central nervous system

Results in experimental model 2 ($\text{ml min}^{-1} 100 \text{ g}^{-1}$), (mean value $\pm$ SE)

Part	Baseline values	15 min after DHE	15 min after dextran 70	At end of expt
Cerebrum				
grey tissue	76 $\pm$ 9	125 $\pm$ 38*	97 $\pm$ 18	83 $\pm$ 19
white tissue	48 $\pm$ 5	75 $\pm$ 18*	63 $\pm$ 9*	57 $\pm$ 11
Cerebellum				
grey tissue	77 $\pm$ 10	131 $\pm$ 30*	106 $\pm$ 16*	91 $\pm$ 19
white tissue	62 $\pm$ 8	103 $\pm$ 25*	86 $\pm$ 13*	72 $\pm$ 16
Thalamus	55 $\pm$ 7	97 $\pm$ 29	73 $\pm$ 14	68 $\pm$ 20
Medulla	63 $\pm$ 12	116 $\pm$ 42	97 $\pm$ 22	90 $\pm$ 28

Significance correlated to baseline values: * $p < 0.05$.

Both dextran 70 and DHE influence central and peripheral haemodynamics. Dextran 70 exerts its effect mainly by increasing plasma volume (Lamke & Liljedahl, 1976; Gruber & Messmer, 1977). DHE increases tonus mainly in capacitance vessels, thereby reducing blood pooling (Mellander & Nordenfelt, 1970) and increasing central blood volume (Mostbeck & Partsch, 1978; Koppenhagen et al., 1979; Reichelt et al., 1980).

In our study, as a result of the plasma volume expansion with dextran 70, cardiac output increased and an overall increase in tissue blood flow to most organs was seen—except for adrenals, genitals, thyroid and central nervous system, where tissue blood flow was unchanged. Thus the increased plasma volume and cardiac output after dextran infusion did not alter the cerebral blood flow. Blood flow to some of the endocrine organs also remained unchanged in spite of increased cardiac output.

The tissue blood flow in the lungs represents the blood flow through the bronchial arteries and arteriovenous shunts permitting the microspheres to return to the lungs where they will be trapped. This flow was unaffected by dextran 70.

DHE reduced blood flow to the pancreas and thyroid, but other endocrine organs were unaffected. Tissue blood flow to the heart (Tables III and IV) was not changed by DHE. This is in agreement with the findings by Schwarz & Kraupp (1979) who found unaltered coronary blood flow in dogs.

The tissue blood flow to all parts of the central nervous system increased after DHE (Table V and VI). Neither angiography nor electromagnetic volume flow recording (vertebral artery) has demonstrated any effects of DHE on cerebral blood flow

in dogs (van den Bergh, 1956; Boismare et al., 1975). With the use of radioactive isotopes, unaltered blood flow and unchanged metabolism in CNS was seen after DHE (Le Poncin-Lafitte & Rapin, 1979). By using radiolabelled microspheres it has been shown that ergotamine does not affect tissue blood flow to the brain (Johnston & Saxena, 1978). Meier-Ruge & Iwangoff (1976) have shown that dihydrogenated ergot alkaloids (and among them DHE) inhibit catecholamine re-uptake (α -receptor blocking activity) and also influence phosphodiesterase activity modifying and reducing the metabolism, especially in nerve endings. Probably DHE also acts by binding to cerebral dopamine and serotonin receptors (Hardebro et al., 1978; Vigouret et al., 1979). Since cerebral metabolism is reduced (Meier-Ruge & Iwangoff, 1976) or at least not increased (Le Poncin-Lafitte & Rapin, 1979) by DHE, the most likely explanation for the increased tissue blood flow to CNS is increased neuronal activity due to the inhibition of neurotransmitter re-uptake. The altered blood pooling achieved by DHE could also affect the autoregulation of cerebral blood flow and be a possible explanation.

This investigation shows that the effect of dextran 70 differs according to whether the vascular bed is pretreated with DHE or not. When it affects vessels, DHE is an α -receptor blocking agent. The plasma volume expansion was not achieved to the same extent when the vascular bed was affected by DHE. The dogs were not splenectomized, which could be one explanation; another might be that DHE increases capillary permeability.

In summary, this investigation has shown that dextran 70 gives an increased tissue blood flow to most organs, but some endocrine organs are unaf-

fect, as also is tissue blood flow to the central nervous system.

DHE gave a reduction of flow to pancreas and thyroid. The increased tissue blood flow to the central nervous system was possibly due to increased neuronal activity or altered autoregulation. Tissue blood flow to the heart was not reduced.

ACKNOWLEDGEMENTS

The valuable support of Dr K-E Arfors and the skilful technical assistance of Gunnel Fredrickson and Claes Lundberg is greatly appreciated.

This study was supported by grants from Sandoz AB, Täby, and Pharmacia AB, Uppsala, Sweden, and the Swedish Medical Research Council (B81-17X-00759-15A).

REFERENCES

- Åberg, M. 1978. On the Effect of Dextran on Lysability and Structure of ex vivo Thrombi, Platelet Function and Factor VIII. Thesis, Malmö.
- Bergenwald, L., Eklund, B., Kaijser, L. & Klingenström, P. 1972. Haemodynamic effect of dihydroergotamine during spinal anaesthesia in man. *Acta Anaesthesiol Scand* 16, 235.
- van den Bergh, R. 1956. L'influence de quelques médicaments usuels sur la vasomotricité carotidienne. Etude artériographique expérimentale. *Acta Neurol Belg* 56, 459.
- Bergqvist, D., Efsing, H. O., Hallböök, T. & Lindblad, B. 1980. Prevention of postoperative thromboembolism. A comparison between dextran 70, dihydroergotamine heparin and a sulphated polysaccharide. *Acta Chir Scand* 142, 243.
- Boismare, F., Hacpille, L., Belliard, J.-P. & Colin, C. 1975. Influence de la dihydroergotamine sur l'hypotension posturale induite, chez le chien, par la lévomépromazine. *J Pharmacol (Paris)* 6, 391.
- Buttermann, G., Theisinger, W., Oechsler, H. & Hör, G. 1975. Untersuchungen über die postoperativen Thromboemboli-Prophylaxe nach einem neuen medikamentösen Behandlungsprinzip. *Dtsch Med Wschr* 41, 2065.
- Castenfors, J., Lindblad, L. E. & Mortasawi, A. 1975. Effect of dihydroergotamine on peripheral circulation during epidural anaesthesia in man. *Acta Anaesthesiol Scand* 19, 79.
- Domenech, R., Hoffman, J., Noble, M., Saunders, K., Hensen, J. & Subijanto, S. 1969. Total and regional coronary blood flow measured by radioactive microspheres in conscious and anaesthetized dogs. *Circ Res* 25, 581.
- Gruber, U. F. & Messmer, K. 1977. Colloids for blood volume support. *Progr Surg* 15, 49.
- Hardebro, J. E., Edvinsson, L., Owman, C. H. & Svendgaard, N. A. 1978. Potentiation and antagonism of serotonin effects on intracranial and extracranial vessels. *Neurology* 28, 64.
- Heymann, M., Payne, B., Hoffman, J. & Rudolph, A. 1977. Blood flow measurements with radionuclide-labelled particles. *Prog Cardiovasc Dis* 20, 55.
- Johnston, B. & Saxena, P. R. 1978. The effect of ergotamine on tissue blood flow and the arteriovenous shunting of radioactive microspheres in the head. *Br J Pharmacol* 63, 541.
- Koppenhagen, K., Vogt, L. & Wenig, H. G. 1979. Dihydroergotamin-Wirkung auf die Lungenperfusion im Akzelerationsstress. *Dtsch Med Wschr* 104, 1208.
- Lamke, L.-O. & Liljedahl, S.-O. 1976. Plasma volume changes after infusion of various plasma expanders. *Resuscitation* 5, 93.
- Le Poncin-Lafitte, M. & Rapin, I. R. 1979. Mise en évidence de l'action cérébrovasculaire des dérivés hydrogénés de l'ergot de siegle chez l'animal jeune et non pathologique. *J Pharmacol (Paris)* 10, 481.
- Lindblad, B. & Bergqvist, D. 1983. Central haemodynamic effects of dextran 70, dihydroergotamine and their combination. A study in dogs. *Acta Chir Scand* 149, 459.
- Meier-Ruge, W. & Iwangoff, P. 1976. Biochemical effects of ergot alkaloids with special reference to the brain. *Postgrad Med J* 52, Suppl. 1, 47.
- Mellander, S. & Nordenfelt, I. 1970. Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. *Clin Sci* 39, 182.
- Mostbeck, A. & Partsch, H. 1978. Umverteilung regionaler Blutvolumina durch Dihydroergotamin und Bein-kompression. *Med Klin* 73, 801.
- Reichelt, W., Pipenbrock, S., Schleussner, E. & Stegmann, T. 1980. Die Wirkungen von Dihydroergotamin auf Volumengehalt und Compliance der extrathorakalen Kapazitätsgefäße des Menschen unter Narkosbedingungen während extrakorporaler Zirkulation in Hypothermie. *Z Kardiol* 69, 67.
- Rudolph, A. & Heymann, M. 1967. The circulation of the fetus in utero. Methods for studying distribution of blood flow, cardiac output and organ blood flow. *Circ Res* 21, 163.
- Sagar, S., Stamatakis, J. D., Higgins, A. F., Nairn, D., Maffei, F. H., Thomas, D. P. & Kakkar, V. V. 1976. Efficacy of low-dose heparin in prevention of extensive deep vein thrombosis in patients undergoing total hip replacement. *Lancet* i, 1151.
- Schossner, R., Arfors, K.-E. & Messmer, K. 1979. MIC-II. A program for the determination of cardiac output, arteriovenous shunt and regional blood flow using the radioactive microsphere method. *Comp Progr Biomed* 9, 19.
- Schwarz, M. & Kraupp, O. 1979. Effects of dihydroergotamine (DHE) on pulmonary and systemic circulation. *Naunyn-Schmiedeberg's Arch of Pharmacol (Berlin)* 308, Suppl. P, R18.
- Vigouret, J.-M., Loew, D. M., Jatton, A.-L. & Markstein, R. 1979. Actions des dérivés de l'ergot de siegle sur le système nerveux central. *J Pharmacol (Paris)* 10, 503.

CHANGES IN PERIPHERAL HAEMODYNAMICS INDUCED BY DEXTRAN 70, DIHYDROERGOTAMINE, AND THEIR COMBINATION. A STUDY USING ULTRASONIC, SERIAL PHLEBOGRAPHY, PLETHYSMOGRAPHY AND ISOTOPE CLEARANCE TECHNIQUES

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SUMMARY:

The aim of this study has been to compare peripheral haemodynamic effects of pharmacological substances used in the prevention of postoperative thromboembolism. Several different techniques were used, with special emphasis on effects on venous circulation. Dextran 70 and dihydroergotamine singly and in combination were evaluated. Dextran 70 increased arterial volume blood flow at rest and during reactive hyperaemia (plethysmography). The arterial and venous vessel cross-sectional area were increased (ultrasound). Clearance from calf veins was unaltered (serial phlebography and isotope technique). Dihydroergotamine reduced reserve vein volume and arterial volume blood flow at rest and during reactive hyperaemia (plethysmography). Crosssectional venous vessel area was reduced and venous blood flow velocity was increased (ultrasound). Clearance from calf veins was unchanged. The combination of dextran 70 and dihydroergotamine did not show additive effects.

INTRODUCTION:

The origin of most deep vein thrombi is in venous cusps and in muscle veins. During anaesthesia and immobilization, the rate of venous blood flow is reduced (2,7,10). The venous flow during anaesthesia tends to be more continuous and almost devoid of pulsatility, making possible large recirculation zones at the venous cusps (11). In these recirculation zones hypoxia develops (9). Both intraoperatively and postoperatively the emptying rate is slow, especially from the calf muscle veins (17). This is because the muscle pump, which is essential for ensuring normal venous circulation in particular in muscle veins, is inactive (1). Such changes as these may be counteracted by thromboprophylactic means, such as the various external compression techniques (2,12,17,21). In addition, pharmacological substances such as dextran 70 and dihydroergotamine have been shown to increase the rate of venous blood flow (6,16,18,20).

The aim of this study has been to study the effects of dextran 70 and dihydroergotamine singly and in combination on peripheral haemodynamics, especially of the venous system. The investigations have been performed in young healthy humans but also in patients in age groups where thromboprophylactic treatment should be considered.

MATERIAL AND METHODS:

This study consists of three separate parts in which different methods were used as listed below:

(1) ON HEALTHY HUMANS:

Ultrasonic measurement of vessel area and blood flow velocity and strain gauge plethysmographic measurement of resting arterial volume blood flow.

(2) ON PATIENTS DURING ANAESTHESIA:

Serial phlebography and contrast clearance from calf veins.

(3) ON PATIENTS AFTER SURGERY:

Strain gauge plethysmography (reserve vein volume, venous emptying, and arterial volume blood flow at rest and during reactive hyperaemia). Isotope clearance from calf veins.

The selected patients without venous or arterial disease had not received thromboembolic prophylactic treatment nor pharmacological therapy which could have interfered with the platelet function. All patients and healthy humans gave their informed consent to participate and the study was approved by the Medical Ethics Committee, University of Lund, Sweden.

PHARMACOTHERAPY:

Dextran 70 (molecular weight 70.000) (Macrodex^R, 6% in NaCl, Pharmacia AB, Uppsala, Sweden) in a dose of 500 ml was infused intravenously over a two hour period. Dihydroergotamine methanesulphonate (Orstanorm^R, Sandoz AB, Täby, Sweden) was given subcutaneously in a dose of 0.5 mg. Combined therapy was given with 500 ml dextran 70 i.v. and 0.5 mg dihydroergotamine s.c. as stated above, at the beginning of the dextran infusion.

INVESTIGATED GROUPS:

In the different parts of this investigation the patients were randomly allocated to one of four groups:

1. Control group - no treatment.
2. Dextran 70 treatment.
3. Dihydroergotamine treatment.
4. Combined therapy with dextran 70 and dihydroergotamine. In the investigation on healthy humans, the four different types of treatment (including controls) were given in random order at one week intervals to all volunteers.

INVESTIGATION OF HEALTHY HUMANS:

Seven healthy humans, four of whom were female, were studied (median age 27, range 24-35; median weight 67 kg, range 53-75). They were given no pharmacotherapy during the investigation period and the two preceding weeks. Before treatment, and two hours after, the following determinations were made: using the strain gauge plethysmographic technique (Elema-Schönander, Swe-

den) with a thigh cuff pressure of 60 mm Hg, resting arterial volume blood flow to the calf was measured; with the bidirectional continuous-wave doppler ultrasound technique (Dopscan 1050, USA), arterial and venous peak blood flow velocity was determined. The doppler probe was kept at an angle of 45° to the direction of blood flow, and this was measured at every application. The blood flow rate was calculated from the formula $V_{\max} = \frac{C \cdot \Delta f}{2 f_0 \cos \delta}$, where $V_{\max}$ = peak flow velocity ($\text{cm} \cdot \text{sec}^{-1}$), C = speed of sound in the medium ($\text{cm} \cdot \text{sec}^{-1}$), Δf = Δ frequency shift (hertz), f_0 = ultrasonic carrier frequency (hertz) and δ = angle between the sonic beam and the velocity vector (22). Measurements in the groin were made at points over the common femoral artery and vein, where the crosssectional area and circumference of the common femoral artery and vein were also determined by the ultrasonic 2-D scanning technique (Diasonics, USA). Each determination was the mean of three recordings. Baseline values were determined after 15 min bed rest. Two hours after therapy was given (or started), and again after 15 min bed rest, another series of measurements were made. Ambient room temperature was kept at 21°C .

INVESTIGATION OF PATIENTS DURING ANAESTHESIA:

20 patients, randomly divided into the four treatment groups, were investigated by a serial phlebography technique. All were over 50 years of age, and undergoing major surgery. No intergroup differences in age, sex or weight were seen. The median age was 72 years (range 57-83), median weight 64 kg (range 56-85), and 13 patients were female. Where pharmacotherapy was indicated by randomization, this was given (or started) at premedication. Where dextran 70-infusion was given, this was completed before the induction of anaesthesia. Anaesthesia was preceded by premedication with atropin and fentanyl (Leptanal^R, Leo AB, Helsingborg, Sweden) and induced with tiopenthal (Pentothal natrium^R, Abbot, Spånga, Sweden). Endotracheal intubation was performed in neuromuscular block induced by pancuronium (Pavulon^R, Organon, V:a Frölunda, Sweden), assisted ventilation was instituted and further fentanyl was then given. After the induction of anaesthesia, but before the start of surgery, a dorsal foot vein on the medial aspect was cannulized and phlebography carried out as follows: Cuffs were placed on the lower thigh and ankle (80 mm Hg, cuffs 15 resp. 7.5 cm wide). After inflation of the cuffs 30 ml metrizamid (Amipaque^R, Nyegaard, Stockholm, Sweden, 170 mg I/ml) was injected and the calf gently compressed for better distribution. A frontal projection X-ray was taken and 60 sec after inflation, the thigh cuff was deflated, a series of X-ray examinations being made 30, 60, 120, 240, 360, 480 and 600 sec after deflation. The time for complete disappearance of contrast from different venous segments such as the deep veins, muscle veins (soleus arcade veins, gastronemicus muscle veins) and superficial veins was determined.

INVESTIGATION OF PATIENTS AFTER SURGERY:

Strain gauge plethysmography was done on 20 patients without associated diseases (divided at random into four groups for investigation). Two days previously they had undergone surgery (appendectomy, cholecystectomy, uretherolithotomy or mammary

surgery). They were fully mobilized but confined to bed for the six hour period during which the plethysmographic evaluation was made. No intergroup differences in age, sex or weight were noted (median age 45 years, range 24-57; median weight 61 kg, range 50-91; 13 were female).

Strain gauge plethysmography was carried out according to Hallböök and Göthlin (4) on both legs (SP2, Medimatic, Denmark). A tourniquet was applied to the thigh just above the knee and well fitted latex gauges filled with mercury were placed around the calf at its largest girth. The position was fixed and the gauges kept in place during the experiment. Resting arterial volume blood flow and reserve vein volume ($\text{ml} \cdot 100 \text{ ml}^{-1} \text{ tissue}$) was obtained with a cuff occlusion pressure of 50 mm Hg, and venous emptying ($\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1} \text{ tissue}$) after rapid, total deflation. After three minutes of arterial occlusion by the cuff (250 mm Hg), and immediate reduction to venous occlusive pressure (50 mm Hg) volume blood flow during reactive hyperaemia was measured. First flow was the flow just after reduction of cuff pressure, and maximum flow recorded under reactive hyperaemia was also noted. Each measurement was repeated three times and the mean values further analyzed.

After baseline values had been recorded, the patients received (or started) therapy according to randomization. Where dextran 70-infusion was given, it was completed within two hours. Measurements were repeated one, three and six hours after the start of the experiments.

Isotope clearance was studied in 40 patients two days after they had undergone surgery (hernial repair, trans-urethral prostatectomy, cholecystectomy, ureterolithotomy and mammary surgery). The patients were randomly allocated to one of the four groups for investigation. No intergroup differences in age, sex or weight were seen (median age 62 years, range 46-85; median weight 69 kg, range 54-94, 15 were female). If indicated, pharmacotherapy was given (or started) two hours before the investigation. A dorsal foot vein on the medial aspect was cannulized. With the patient in bed rest, a tourniquet was applied to the distal thigh and to the ankle (pressure 80 mm Hg, 15 resp. 7.5 cm wide cuff). After inflation of the cuffs, 20 MBq ^{99}Tc labelled macro-aggregated human albumin (Amersham, England) was injected, followed by an injection of 10 ml saline, calf was gently compressed for better distribution. A collimated 2" x 2" detector was placed against the thickest part of the calf. The thigh cuff was deflated one minute after inflation, and the decrease in activity was continuously monitored for ten to fifteen minutes by a scintillation counter (Necab, USA), initial activity being set at 100%. The decrease in activity after 15, 30, 60, 120, 240 and 480 sec were evaluated.

STATISTICAL CALCULATIONS:

Statistical calculations were made using the Student t-test for paired and unpaired observations, and the Mann-Whitney rank sum test. Values where $p < 0.05$ were considered significant.

RESULTS

Healthy humans

Dextran 70 infusion increased resting volume blood flow (+68%) (Table I) which was also reflected in increased arterial cross-sectional vessel area (+42%), while the arterial blood flow velocity remained unchanged (+10%) (Table II and III). The venous blood flow velocity was unchanged after dextran 70 infusion (+4%), but venous vessel cross-sectional area increased (+40%). Dihydroergotamine reduced volume blood flow to the calf (-24%) (Table I). Dihydroergotamine decreased venous vessel area (-21%) (Table III), and increased venous blood flow velocity (+41%) (Table II), but arterial vessel area and arterial blood flow velocity were unchanged. The combination of dextran 70 and dihydroergotamine resulted in a tendency of increased venous blood flow velocity (+24%) and decreased venous vessel area (-20%) (Table III), other variables being largely unaffected.

During anaesthesia

Serial phlebography, made under general anaesthesia, showed good initial filling of the calf veins. Deep calf veins were cleared of contrast within one to two minutes of thigh cuff deflation. Though muscle veins were not completely free of contrast within the ten minute observation period, and in no case was the soleus arcade vein emptied, in most cases the gastrocnemius muscle veins and superficial veins were completely clear. There was no difference in clearance between the four groups of patients. Fig. 1 shows an example of contrast clearance.

TABLE I. Resting arterial blood flow to the calfs in healthy humans and postoperative patients.

Healthy humans (n=7; mean $\pm$ SEM, ml $\cdot$ min⁻¹ $\cdot$ 100 ml⁻¹).

	Baseline recordings	After 2 hours
Control	3.9 $\pm$ 1.3	4.4 $\pm$ 1.5
Dextran 70	3.5 $\pm$ 1.3	5.9 $\pm$ 2.8**
Dihydroergotamine	4.1 $\pm$ 1.6	3.2 $\pm$ 1.7***
Dextran 70 + dihydroergotamine	4.1 $\pm$ 1.3	3.7 $\pm$ 1.7

Postoperative patients (n=20; mean $\pm$ SEM, ml $\cdot$ min⁻¹ $\cdot$ 100 ml⁻¹).

	Baseline recordings	Hours after administration of substances		
		1	3	6
Control	3.4 $\pm$ 0.3	3.3 $\pm$ 0.3	3.5 $\pm$ 0.3	3.3 $\pm$ 0.4 *
Dextran 70	3.3 $\pm$ 0.3	3.8 $\pm$ 0.4***	4.1 $\pm$ 0.5*	4.7 $\pm$ 0.3
Dihydroergotamine	3.7 $\pm$ 0.4	2.8 $\pm$ 0.3**	2.6 $\pm$ 0.2**	3.4 $\pm$ 0.3
Dextran 70 + dihydroergotamine	3.2 $\pm$ 0.4	3.0 $\pm$ 0.6	3.2 $\pm$ 0.3	3.5 $\pm$ 0.3

* p<0.05; ** p<0.02; *** p<0.01.

TABLE II. Arterial and venous peak blood flow rate in healthy humans (n=7, mean $\pm$ SEM).

	Arterial peak flow velocity (cm $\cdot$ sec $^{-1}$)	
	Baseline recordings	After 2 hours
Control	60 $\pm$ 14	58 $\pm$ 8
Dextran 70	66 $\pm$ 11	73 $\pm$ 8
Dihydroergotamine	61 $\pm$ 8	62 $\pm$ 10
Dextran 70 + dihydroergotamine	64 $\pm$ 7	69 $\pm$ 7
	Venous peak flow rate (cm $\cdot$ sec $^{-1}$)	
	Baseline recordings	After 2 hours
Control	56 $\pm$ 10	55 $\pm$ 16
Dextran 70	58 $\pm$ 16	61 $\pm$ 24
Dihydroergotamine	49 $\pm$ 8	69 $\pm$ 23*
Dextran 70 + dihydroergotamine	50 $\pm$ 18	62 $\pm$ 23

* p<0.05

TABLE III. Arterial and venous vessel cross-sectional area in healthy humans (n=7, mean $\pm$ SEM).

	Arterial vessel area (cm 2)	
	Baseline recordings	After 2 hours
Control	0.72 $\pm$ 0.22	0.71 $\pm$ 0.24
Dextran 70	0.54 $\pm$ 0.15	0.77 $\pm$ 0.25**
Dihydroergotamine	0.52 $\pm$ 0.10	0.55 $\pm$ 0.13
Dextran 70 + dihydroergotamine	0.64 $\pm$ 0.22	0.65 $\pm$ 0.22
	Venous vessel area (cm 2)	
	Baseline recordings	After 2 hours
Control	0.63 $\pm$ 0.14	0.59 $\pm$ 0.17
Dextran 70	0.62 $\pm$ 0.14	0.87 $\pm$ 0.19***
Dihydroergotamine	0.64 $\pm$ 0.17	0.51 $\pm$ 0.08**
Dextran 70 + dihydroergotamine	0.68 $\pm$ 0.12	0.54 $\pm$ 0.14

* p<0.05; ** p<0.2; *** p<0.01.

Postoperative studies

Two techniques were used in the postoperative studies. Plethysmography showed at rest and during reactive hyperaemia an increase in arterial volume blood flow that persisted for the six hour observation period after dextran 70 infusion ($p < 0.01$), and a decrease after dihydroergotamine treatment ($p < 0.05$) (Fig. 2). Reserve vein volume increased during bed rest in the control group (13%) ($p < 0.01$), compared with the reduction (9%) seen in patients treated with dihydroergotamine ($p < 0.01$), both changes persisting for the six hour period of investigation (Fig. 3). Venous emptying remained largely unchanged in all groups, except for a reduction in patients treated with dihydroergotamine ($p < 0.05$) that persisted throughout the experiments ($p < 0.01$) (Fig. 4). The isotope clearance study showed an abrupt reduction in activity immediately after thigh cuff deflation, followed by a slow, steady decrease that in most cases was still incomplete when ten minutes had elapsed (Table IV). No difference between the investigated groups was seen.

Table IV: Isotope clearance from calf veins. Reduction in percent of initial activity (100%), (n=40; % activity $\pm$ SEM).

Group	Reduction in activity (%)					
	15	30	60	120	240	480 sec.
Control	44 $\pm$ 6	58 $\pm$ 6	68 $\pm$ 6	77 $\pm$ 5	84 $\pm$ 4	87 $\pm$ 4
Dextran 70	50 $\pm$ 5	67 $\pm$ 5	74 $\pm$ 5	81 $\pm$ 3	88 $\pm$ 3	90 $\pm$ 3
Dihydroergotamine	49 $\pm$ 6	64 $\pm$ 5	70 $\pm$ 5	76 $\pm$ 5	81 $\pm$ 5	85 $\pm$ 4
Dextran 70 + dihydroergotamine	34 $\pm$ 7	51 $\pm$ 6	62 $\pm$ 4	74 $\pm$ 3	83 $\pm$ 2	88 $\pm$ 2

DISCUSSION

"Venous stasis" is one of the pathogenic factors in the development of postoperative deep vein thrombosis but the term is rather ill-defined. To avoid misunderstanding alterations in volume flow and flow velocity should be interpreted separately. The clearance from veins, resulting from the combined influence of volume and velocity of blood flow, differs between different venous segments. The clearance of calf muscle veins is slow at least during anaesthesia (17). It is important to add evaluation of clearance when studying haemodynamic alterations that predispose for thrombus formation.

No golden standard method exists for optimal evaluation of the venous circulation, and methodology in studies of venous haemodynamics is far less standardized than in studies of arterial haemodynamics. Previous investigations of both dextran and dihydroergotamine have almost exclusively been restricted to analysis

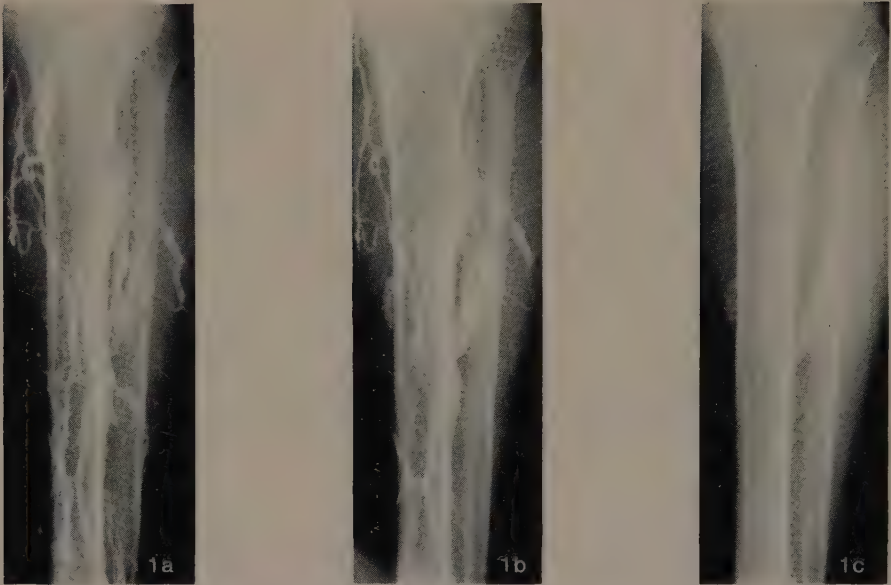


Fig 1 a-c: Contrast clearance from calf veins in a patient given dextran 70 before investigation. a: initial filling of veins, b: 30 s after thigh cuff deflation, c: 10 min after deflation.

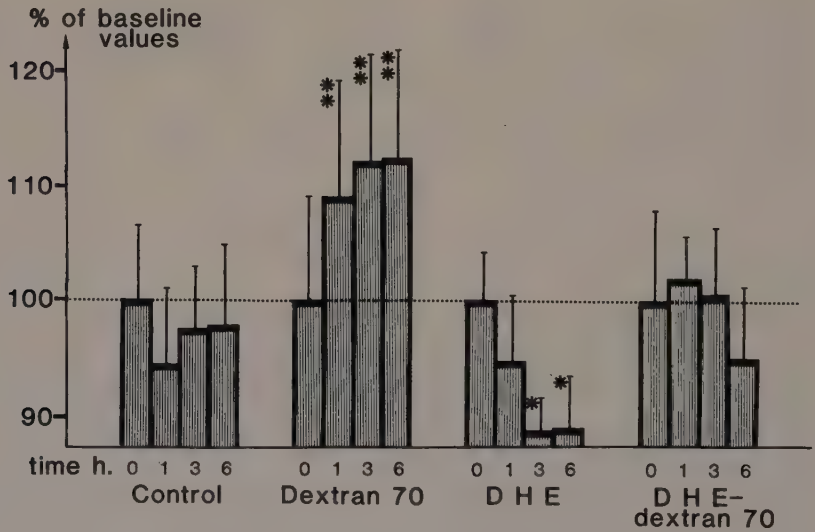


Fig 2. Maximal arterial blood flow changes (%) in patients postoperatively during reactive hyperaemia during a six hour bed rest and different treatments (* $p < 0.05$; ** $p < 0.01$).

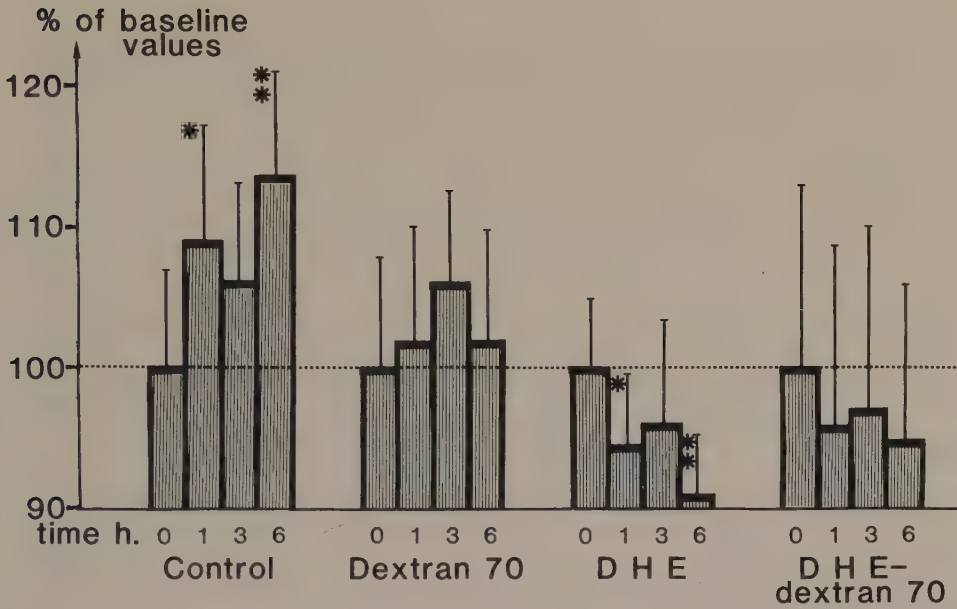


Fig 3. Reserve vein volume changes (%) in patients postoperatively during a six hour bed rest and different treatments (* $p < 0.05$; ** $p < 0.01$).

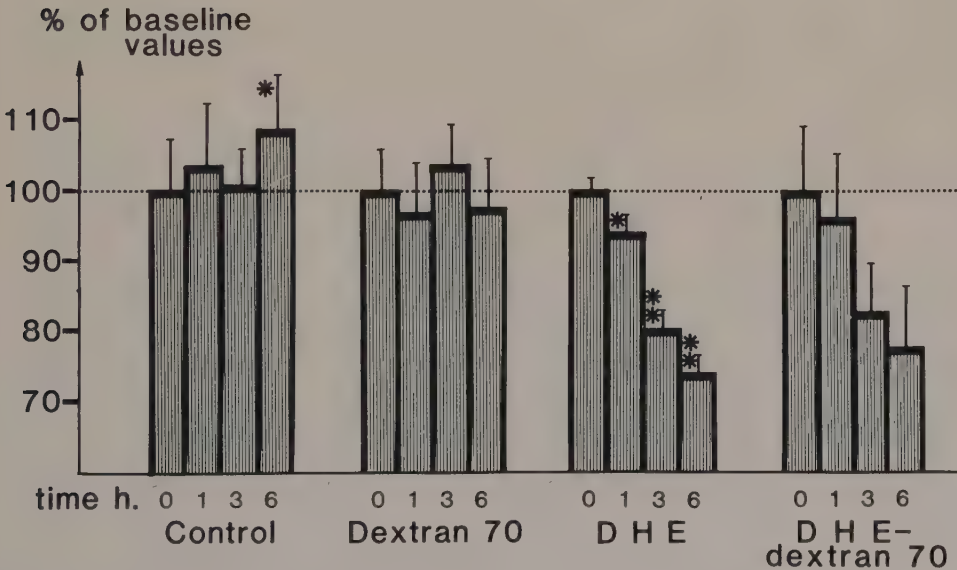


Fig 4. Venous emptying changes (%) in patients postoperatively during a six hour bed rest and different treatments (* $p < 0.05$; ** $p < 0.01$).

of one function. Since the aim of this study was to evaluate the thromboprophylactic role of these substances and their combination it was considered necessary to use several methods. This gave a more complete picture of the influence on venous function. As there has been some discussion whether or not thromboprophylaxis with dihydroergotamine can induce arterial vasospasm as a potentially dangerous complication it was also considered necessary to measure arterial flow. Limitations and technical errors of the methods used have been reviewed by Strandness and Sumner (22). Contrast medium clearance by phlebographic technique permits an anatomic evaluation which is impossible with clearance of injected isotopes. We used human macro-aggregated albumin labelled with ^{99}Tc whereby recirculation was avoided. Neither contrast medium nor labelled proteins guarantee a rheologic situation similar to that of blood, but they are the methods currently used for evaluating calf vein performance during complete or almost complete muscle relaxation (17).

In the control group reserve vein volume increased during bed rest implicating vasodilatation, a finding reported previously (19). In the healthy humans cross-sectional area was unchanged, but they had not been confined to bed rest between the measurements.

Dextran 70 infusion increased arterial volume blood flow both in healthy humans and in patients after surgery. In the healthy humans arterial vessel area increased in combination with unchanged blood flow velocity, indicating an increased arterial volume blood flow. In animal experiments dextran increased venous volume blood flow measured electromagnetically (13) and tissue blood flow to the muscles determined with labelled microspheres (14). Plethysmographically dextran did not alter reserve vein volume or venous emptying which is in accordance with the data from the clearance studies, but in the healthy humans an increased venous vessel area and unchanged blood flow velocity indicated an increased venous volume blood flow.

Reasons for this discrepancy in venous volume blood flow with the methods used in this study could be: A: the different methods do only obtain indirect information of volume blood flow and do not give equivalent and entirely comparable data, B: there is a decreased venous distensibility with increasing age (22), and C: dextran infusion induces a certain degree of hypervolaemia in healthy volunteers whereas the operated patients could be normo- or hypovolaemic.

The difference between unchanged contrast medium clearance and indications of increased venous volume blood flow in healthy humans after infusion of dextran 70 could also be an anaesthetic effect in patients undergoing contrast medium clearance. However, the results of contrast medium clearance in anaesthetized patients are very similar to those of the isotope clearance investigation which also fits with the unchanged venous emptying measured plethysmographically in unanaesthetized patients in otherwise similar conditions. Unchanged clearance could be due to changes in the volume to be cleared. Increased volume blood

flow will not alter clearance if the volume to be cleared is increased. In addition to the reasons for the discrepancy in recordings reflecting volume changes given above dextran may open AV-shunts, or the increased venous volume blood flow obtained by dextran is transported in a few "main veins" but other venous segments have an unchanged volume blood flow according to the theory of Jansen (6). However, alterations in volume blood flow are suggested to be of less importance than flow velocity changes in counteracting thrombus formation (22).

Dextran 70 "improves the microcirculation" by reducing viscosity (23) and perhaps by passive capillary dilatation (5). These changes could be of greater importance than the "macrocirculatory" effect of dextran 70 in preventing thrombus formation.

Dihydroergotamine gave a reduction in reserve vein volume and thereby also venous emptying rate as well as increased blood flow velocity in the veins, and a reduction in venous vessel cross-sectional area was seen. These findings are in accordance with other findings (3,8,10,15,16,20,24). However, calf clearance did not differ from that in controls. Dihydroergotamine reduced arterial volume blood flow measured plethysmographically, but in the healthy humans both arterial vessel area and peak blood flow velocity were unchanged. This suggests a discrepancy in findings between the two methods, but peak blood flow velocity and vessel area only indicate the volume blood flow.

The combination of dihydroergotamine and dextran 70 resulted in no major additive effect on venous function. Venous blood flow velocity increased but not significantly. Venous vessel area was slightly reduced. Volume recordings and clearance studies were unaltered. Since no increase in vessel cross-sectional area was obtained by dextran 70 infusion it seems as the constrictive effect of dihydroergotamine dominates. Perhaps the constrictive effect of dihydroergotamine, most pronounced in veins but also seen in arterioles, also prevents "the microcirculatory improvement" otherwise caused by dextran 70.

To conclude our study showed that pharmacologic regimens counteracting thrombus formation interact with peripheral haemodynamics. Dextran 70 increased volume blood flow. Dihydroergotamine reduced reserve vein volume, and increased venous blood flow velocity probably by decreasing venous vessel cross-sectional area. The beneficial haemodynamic effects from a thromboprophylactic point of view of dextran 70 and dihydroergotamine are not additive when they are used in combination. Neither dextran 70 nor dihydroergotamine, singly or in combination, improved clearance of contrast medium or radiolabelled macroaggregated albumin from the calf veins.

ACKNOWLEDGEMENTS:

The skilful technical assistance of Lisbet Karlsson, Christina Cederlund and Gudrun Jungqvist has been greatly appreciated. A grant was provided from the Swedish Medical Research Council (00759).

Bibliography

- (1) Almén,T., Nylander,G.: Serial phlebography of the normal lower leg during muscular contraction and relaxation. *Acta Radiol* 57,264, 1962.
- (2) Becker,J., Schampi,B.: The incidence of postoperative venous thrombosis of the legs. A comparative study on the prophylactic effect of dextran 70 and electrical calf-muscle stimulation. *Acta Chir Scand* 139,357, 1973.
- (3) Felix,R., Louven, B.: Zur Vasoaktivität von Dihydroergotamin. *Phlebographische Untersuchungen. Fortschr Med* 90,757, 1972.
- (4) Hallböök,T., Göthlin,J.: Strain gauge plethysmography and phlebography in diagnosis of deep vein thrombosis. *Acta Chir Scand* 137,37, 1971.
- (5) Hint,H.: The flow properties of erythrocyte suspensions in isolated rabbit's ear, the effects of erythrocyte aggregation, haematocrit and perfusion pressure. *Bibl Anat* 4,112, 1964.
- (6) Jansen,H.: Postoperative thromboembolism and its prevention with 500 ml dextran given during operation. With a special study of the venous flow pattern in the lower extremities. *Acta Chir Scand (Suppl)* 427, 1972.
- (7) Jönsson,G.: Venous circulation in the lower half of the body. A clinico-experimental study with special reference to the postoperative phase. *Acta Chir Scand (Suppl)* 161, 1951.
- (8) Kakkar,V.V.: Knowledge and perspective of thromboembolic research. In: *Postoperative Thromboembolie-Prophylaxe aus aktueller Sicht*. Eds Tscherne,H., Deutsch,E.. Georg Thieme Verlag, Stuttgart, New York. 1981, p 1.
- (9) Karino,T.: Possible function of vortices as automatic traps and generators of thrombi. *Thromb Haemost* 50, 68, 1983.
- (10) Kunz,S., Burth,O.M., Zimmerer,E.: Assessment of venous function after major gynecological surgery with heparin-dihydroergotamine in the prophylaxis of DVT. *Thrombos Haemostas* 46,190, 1981.
- (11) Lewis,C., Mueller,C., Edwards,S.: Venous stasis on the operating table. *Am J Surg* 124,780, 1972.
- (12) Lewis,C., Antoine,J., Mueller,C., Talbot,W., Swaroop,R., Edwards,S.: Elastic compression in the prevention of venous stasis. A critical reevaluation. *Am J Surg* 132,739, 1976.
- (13) Lindblad,B., Bergqvist,D.: Central haemodynamic effects of dextran 70, dihydroergotamine and their combination. A study in dogs. *Acta Chir Scand* 149, 459, 1983.
- (14) Lindblad,B., Bergqvist,D.: Tissue blood flow and blood flow distribution after administration of dextran 70, dihydroergotamine and their combination. A study in dogs using the radioactive microsphere technique. *Acta Chir Scand* 149, 467, 1983.
- (15) Mellander,S., Nordenfelt,I.: Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. *Clin Sci* 39,183, 1970.
- (16) Mühe,E., Burghardt,K-H., Kolb,W., Strobel,G.: Eine neue Methode zur Prophylaxe postoperativer Venethrombosen. *Klinikerzt* 4,88, 1975.

- (17) Nicolaides, A.N., Kakkar, V.V., Field, E.S., Fish, P.: Soleal veins, stasis and prevention of deep vein thrombosis. In: Thromboembolism: diagnosis and treatment. Eds. Kakkar, V.V., Jouhar, A.J.. Churchill Livingstone, Edinburgh, London. 1972
- (18) Partsch, H., Kahn, P.: Venöse Strömungsbeschleunigung in Bein und Becken durch "Anti-Thrombose-Strümpfe". Klinikarzt 11,3, 1982.
- (19) Pauschinger, P., Matis, P., Rieckert, H.: Die Veränderung der Durchblutung im Bereich der unteren Extremität infolge Inaktivität und ihre Beeinflussung durch Trasylol. Med Welt 51,2822, 1968.
- (20) Rieckert, H.: Primäre Therapieziele bei der hypotonen Fehlregulation. Fortschr Med 89,173, 1971.
- (21) Sigel, B., Edelstein, A., Savitch, L., Hasty, J., Felix, R.: Type of compression for reducing venous stasis. A study of lower extremities during inactive recumbency. Arch Surg 110,171, 1975.
- (22) Strandness, D.E., Sumner, D.S.: Hemodynamics for surgeons. Grune & Stratton, New York, San Francisco, London. 1975.
- (23) Thorén, L.: Dextran as a plasma volume substitute. Progr Clin Biol Res 19,265, 1978.
- (24) Ulrich, J., Jessen, B., Siggaard-Andersen, J.: Comparative effects of dihydroergotamine and hydergin on the blood flow, capillary filtration rate and the capacitance vessels in the human calf studied by plethysmography. Angiologia 24,657, 1973.

The Pharmacokinetics of Subcutaneous Dihydroergotamine with and without a Dextran 70 Infusion

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Summary. The pharmacokinetics of subcutaneous dihydroergotamine (DHE) with or without dextran 70 infusion was evaluated in a single- and multiple-dose study in 30 patients. Radioimmunoassay was used to measure plasma DHE and the anthrone method to determine the dextran concentration. In the single-dose study no significant interaction between DHE and dextran was noted with respect to their plasma levels. The absorption of s.c. DHE was rapid and the disappearance curve followed a biphasic pattern, $t_{0.5\alpha}$ being 1.4 and 2.0 h, $t_{0.5\beta}$ 22 and 21 h for DHE and DHE/dextran 70, respectively. In the multi-dose study the trough level of DHE initially had a tendency to rise, in accordance with simulated plasma concentration curves. DHE trough levels were about 0.5 ng/ml and were well above the assumed minimum effective value to induce venoconstriction (0.06 ng/ml). Dextran concentrations were significantly higher when DHE was co-administered, possibly, due to changes in plasma volume. It is concluded that DHE 0.5 mg s.c. twice daily will give an adequate plasma concentration and that there was no important interaction between it and infused dextran 70.

Key words: dihydroergotamine, dextran 70; pharmacokinetics, radioimmunoassay, drug interaction

Dihydroergotamine (DHE), especially when combined with low-dose heparin, is effective in reducing postoperative thromboembolic complications (Sagar et al. 1976; Stamatakis et al. 1977; Bergqvist et al. 1980). The bioavailability of orally administered DHE is low and variable due to incomplete absorption (Aellig and Nüesch 1977) and extensive first-

pass metabolism (Little et al. 1982). However, in prophylactic treatment against thromboembolism it is given subcutaneously. The pharmacokinetics of subcutaneous DHE in patients has not been established, nor has any investigation been made into whether DHE accumulates when repeated s.c. injections are given.

Dextran 70 (molecular weight 70,000) has also been shown to reduce postoperative thromboembolism when given intravenously. As its mechanism of action differs at least in part from that of DHE (Lange and Echt, 1972; Thorén 1978), a combination of DHE and dextran might be beneficial in preventing postoperative thromboembolism. Before assessing the efficacy of this combination, a pharmacokinetic analysis is essential. The present investigation was done to evaluate the pharmacokinetics of subcutaneous DHE alone and in combination with dextran 70 infusions, and to determine whether repeated subcutaneous injection of DHE would result in its accumulation.

Material and Methods

Subjects

The study was divided into two experiments:

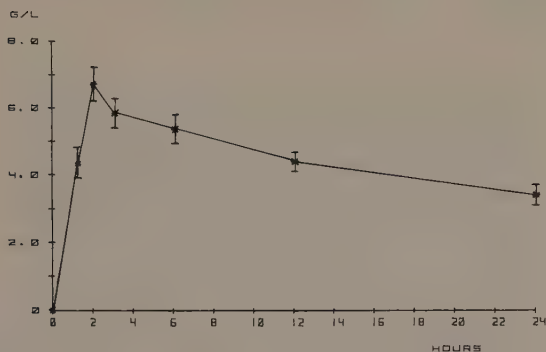
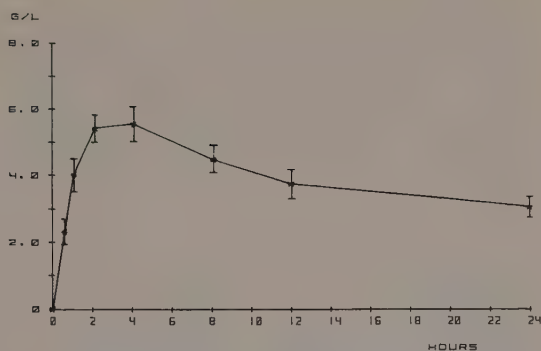
1. Single-dose administration of DHE and dextran 70, and their combination.
2. Multiple-dose administration of DHE and dextran 70, and their combination.

Each type of treatment was examined in five patients, making a total of 30 patients in the study.

Patients in the first experiment had undergone surgery two days prior to the pharmacokinetic investigation (appendectomy or mammary, gallbladder or ureteral stone surgery). The risk of developing post-

Table 1. Details of patients studied

	Mean age [years] (range)	Mean weight [kg] (range)	Median peroperative blood loss [ml] (range)	Median postoperative transfusion requirements. Units (range) (1 unit = 400 ml blood)
<i>Experiment 1: single-dose administration</i>				
DHE s.c.	36 (28–46)	65 (56–84)	100 (0–250)	0
Dextran 70 i.v.	50 (30–60)	70 (55–91)	0 (0–300)	0
Combination	40 (24–55)	75 (54–89)	100 (0–300)	0
<i>Experiment 2: multiple-dose administration</i>				
DHE s.c.	64 (50–81)	71 (52–85)	450 (250–1000)	2 (0–4)
Dextran 70 i.v.	65 (55–78)	73 (54–87)	500 (250–1400)	2 (0–4)
Combination	72 (65–77)	73 (54–90)	475 (250–1400)	2 (0–4)

**Fig. 1.** Plasma concentrations of dextran after infusion of 6% dextran 70 500 ml (mean ± SEM)**Fig. 2.** Plasma concentration of dextran after infusion of 6% dextran 70 500 ml and s.c. injection of DHE 0.5 mg (mean ± SEM)

operative thromboembolism was considered low, so prophylactic therapy was not given. None of the patients had known associated diseases or were receiving chronic pharmacotherapy. Blood loss was minimal during surgery, and no patient needed blood transfusion pre-, per- or postoperatively. The pat-

ients were mobilized at least 12 h prior to the investigation. No drug was allowed during the study period. A comparison of the patients in the two groups in Model 1 is given in Table 1.

In experimental Model 2, patients were chosen who had undergone elective hip arthroplasty, and in whom prophylactic treatment against thromboembolism was indicated. The patients were older than those in Experiment 1. They had no known associated diseases and none were on chronic drug treatment. Morphine hydrochloride or paracetamol was given for postoperative analgesia. A comparison between the groups in Experiment 2, including blood loss and transfusion requirements, is also presented in Table 1.

Each patient gave her/his written consent to participate in the study and it was approved by the Ethical Committee of the University of Lund.

Trial Design

Dihydroergotamine methanesulphonate 0.5 mg (Orstanorm®, 1.0 mg/ml, Sandoz AB, Täby, Sweden) was given subcutaneously in the lateral aspect of the thigh.

Dextran 70 (Macrodex® 6% in saline, Pharmacia AB, Uppsala, Sweden) was given intravenously, each infusion of 500 ml being given over 2 h. The infusion was given in the arm opposite to that from which blood samples were taken.

In Experiment 1, single doses of DHE 0.5 mg, 6% dextran 70 500 ml in saline, and their combination were given, and blood samples were taken before and on repeated occasions during the 24 h after the administration (Figs. 1–4).

In Experiment 2 repeated doses were given. DHE 0.5 mg s.c. was started at 8 p.m. on the day before operation and was maintained for 5 days – 12-hourly administration at 8 a.m. and p.m. Dextran 70 500 ml was given peroperatively followed by a further 500 ml within 12 h after the end of the operation.

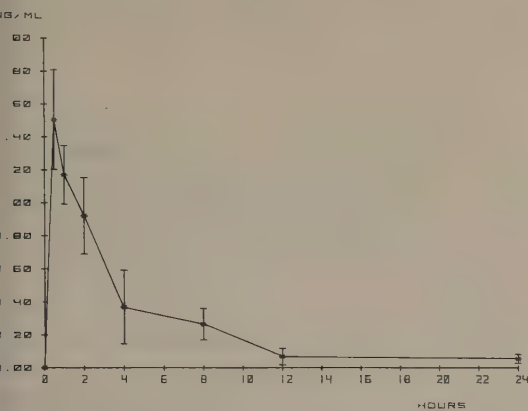


Fig. 3. Plasma concentrations of DHE after DHE 0.5 mg s.c. (mean $\pm$ SEM)

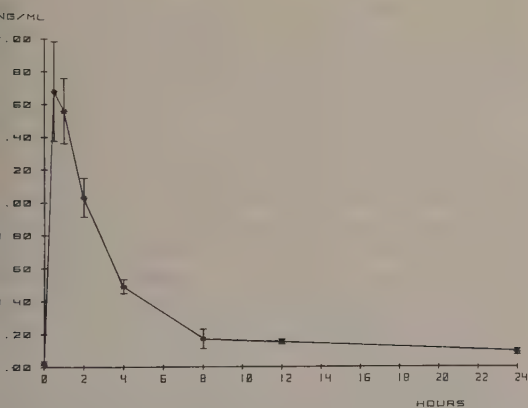


Fig. 4. Plasma concentrations of DHE after DHE 0.5 mg s.c. and infusion of 6% dextran 70 500 ml (mean $\pm$ SEM)

An additional 500 ml dextran was given on the first and third postoperative days, starting at 8 a.m.

Blood samples were taken prior to administration of the drugs and then on each morning of the first 4 postoperative days, 30 min before the time of the next dose (Figs. 5, 6).

The blood samples were collected in lithium heparin tubes for DHE measurement and in citrate tubes for assay of dextran. They were immediately centrifuged and the plasma separated and stored at -20°C until analysed.

Assay Methods

The concentration of DHE was determined by radioimmunoassay technique (Rosenthaler and Munzer

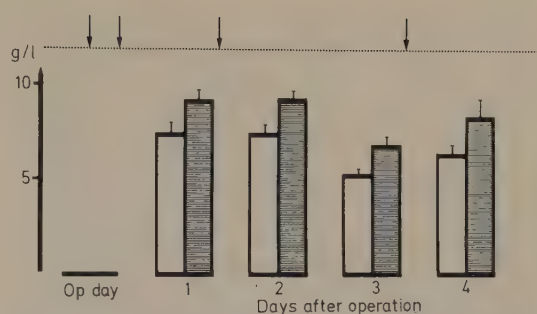


Fig. 5. Trough plasma levels of dextran during the multiple-dose study (mean $\pm$ SEM). Each administration is indicated by an arrow; the shaded bars represent the combined therapy group

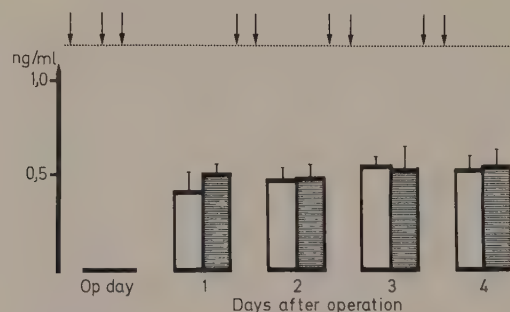


Fig. 6. Trough plasma levels of DHE during the multiple-dose study (mean $\pm$ SEM). Each administration is indicated by an arrow; the shaded bars represent the combined therapy group

1976), using a specific rabbit antiserum (Batch 180380) with a detection limit of ~ 0.05 ng/ml.

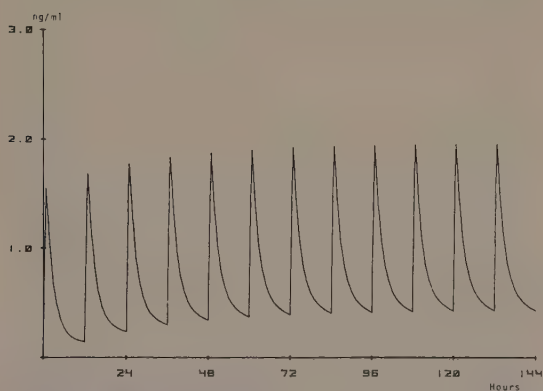
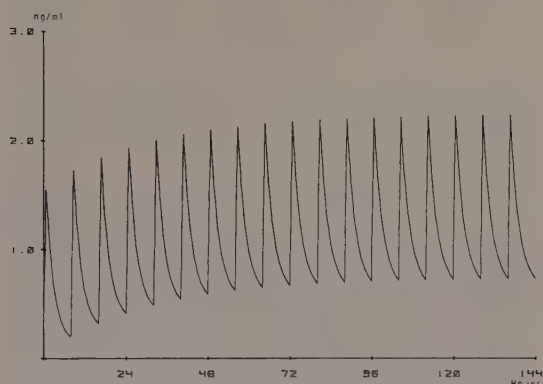
Dextran was determined by the anthrone method of Jenner (1967); the detection limit was 0.06 g/l.

Kinetic Calculations

AUC (area under the curve) from 0–8 and 0–24 h, $C_{\max}$ (concentration maximum) and $T_{\max}$ (time for maximum) were calculated from the individual raw data. The absorption and elimination parameters, expressed as $t_{0.5}$ absorption, $t_{0.5}$ α - and β -elimination phase, were calculated from the mean values using $1/\text{SD}$ for weighting. The mean plasma concentration-time curve for each experiment was fitted to an equation with 3 exponential terms, for the absorp-

Table 2. Pharmacokinetic parameters ($\pm$ SEM) of subcutaneously administered dihydroergotamine 0.5 mg

		DHE s.c. ^a	DHE s.c. + dextran inf.
$C_{\max}$	[ng/ml]	1.74 ± 0.30	1.54 ± 0.30^a
$t_{\max}$	[h]	0.7 ± 0.1	0.8 ± 0.3^a
$t_{0.5}$ absorption	[h]	0.17	0.07
$t_{0.5}$ α -phase	[h]	1.39	2.01
$t_{0.5}$ β -phase	[h]	22.2	20.6
$AUC_{(0-8)}$	[ng/ml/h]	7.35 ± 0.59	4.52 ± 1.40^b
$AUC_{(0-24)}$	[ng/ml/h]	7.5 ± 0.79	5.98 ± 1.99^b

^a $n = 5$; ^b $n = 4$ **Fig. 7.** Simulated plasma concentration curve for administration of DHE 0.5 mg/12-hourly**Fig. 8.** Simulated plasma concentration curve for administration of DHE 0.5 mg/8-hourly

tion, the α - and β -elimination phase. Program ELSFIT (Sheiner 1981) on an HP-1000 computer was used for the least squares fit. Curves simulated with the pharmacokinetic parameters from the single dose study were prepared for twice daily and three times

daily subcutaneous administration of dihydroergotamine.

Statistical Analysis

The significance of differences was assessed by Student's *t*-test for paired observations, and Mann-Whitney's rank sum test for unpaired observations. The level of significance chosen was $p < 0.05$.

Results

The results of the single-dose administration are presented in Figs. 1–4. The dextran concentration reached a maximum immediately after the end of infusion, and then a slow decrease was found with a half-life of 23 h; the half-life with DHE was 24 h. No significant interaction between dextran and DHE was found with respect to the dextran level, as judged by the absence of a significant difference in peak concentration, half-life and AUC-value.

DHE (Figs. 3, 4) was rapidly absorbed following subcutaneous administration. The disappearance curve followed a biphasic pattern, with a rapid α -phase and a slow β -phase. The half-life for the α -phase was 1.4 h for DHE alone and 2.0 h when combined with dextran; for the β -phase the values were 22 and 21 h, respectively. No significant interaction between dextran and DHE was noted with respect to DHE level, as judged by the absence of a significant difference in peak concentration, half-life and AUC-value (Table 2).

In Experiment 2, the trough levels for DHE and dextran were followed (Figs. 5, 6). Dextran concentrations were approximately 2 g/l higher when DHE was co-administered ($p < 0.05$ on postoperative Days 1 and 2, and $p < 0.01$ on postoperative Day 3). There was no difference in DHE level between the group receiving DHE alone and that receiving the combination of DHE and dextran 70.

The trough levels of DHE did not increase significantly during treatment, but in most cases the trough level had a tendency to rise during the first three postoperative days. This is in accordance with the simulated curves for DHE administered s.c. twice and thrice daily calculated from the pharmacokinetic parameters obtained for the single-dose administration of DHE (Figs. 7, 8).

Discussion

Dihydrogenation of naturally occurring ergot alkaloids has led to the development of dihydroergota-

mine (DHE). DHE has mainly been used for the prevention of migraine and in the treatment and prevention of orthostatism and hypotension. Recently the beneficial effect of DHE in preventing postoperative thromboembolism has been noted (Buttermann et al. 1975; Mühe et al. 1975), especially when combined with low-dose heparin (Sagar et al. 1976; Kunz et al. 1977; Stamatakis et al. 1977; Bergqvist et al. 1980). For prophylaxis DHE is given subcutaneously in the dose of 0.5 mg (Lange and Echt 1972), administered two or three times daily (Mühe et al. 1975). The pharmacokinetics of subcutaneous DHE has not previously been analysed, and it was also not known if DHE were to accumulate after repeated subcutaneous injections.

A radioimmunoassay technique was used to measure DHE concentrations: the detection limit was 0.05 ng/ml.

The present study was based on patients who were about to or had already undergone surgery. The number of blood samples it was possible to obtain was smaller than that which could have been collected from young volunteers, which means that some inaccuracy in the determined pharmacokinetic parameters is possible.

The pharmacokinetics of DHE has been analysed after oral and intravenous administration using a radioactive preparation (Meier and Schreier 1976; Aellig and Nüesch 1977; Bobik et al. 1980). This technique has higher sensitivity but the specificity is low since radioactive metabolites are also measured. Hilke et al. (1978) used a different RIA-technique with a lower sensitivity than the method used here. Olver et al. (1980) used the same technique as us, but presented data for only two patients. Comparison of the present of previously published results is not really possible.

Using the same technique as us, Little et al. (1982) presented pharmacokinetic data after intravenous and oral administration to healthy volunteers. After i. v. administration, the main part of the plasma DHE curve declined with a $t_{0.5}$ of about 2.4 h, which is comparable to the value of about 1.4 h after s. c. injection reported here. The slower terminal half-life of the very small fraction of DHE which remained in the plasma could not be detected in the i. v. study, as plasma levels were only followed for 8 h.

Absorption after subcutaneous administration mainly depends on the solubility of the drug and tissue blood flow in the area where the drug is injected. DHE showed rapid absorption, and maximum plasma concentrations were mostly found within 30 min after administration (7 out of 10 patients).

In the multiple-dose study with 12 h dosing intervals trough levels after the second daily s. c. injection

of DHE revealed no tendency to accumulation of DHE. Trough levels were about 0.5 ng/ml, well above the assumed minimum effective value of 0.06 ng/ml (Müller-Schweinitzer 1980). Trough levels after 120 h simulated from the single-dose pharmacokinetic parameters were about 0.44 ng/ml for twice daily and 0.65 ng/ml for three times daily s. c. administration of DHE.

Single-dose administration of dextran 70 led to the maximum plasma concentration at the end of the 2 h infusion. A slow decline in plasma concentrations was found thereafter, as reported by others (Lamke and Liljedahl 1976; Åberg et al. 1977; Thorén 1978).

When repeated dextran infusions were given the trough levels ranged from 5.22 to 7.45 g/l. With combined DHE/dextran therapy, trough levels of dextran after repeated infusions ranged from 7.22 to 9.45 g/l, i.e. they were within the effective range (Åberg et al. 1977).

There were no differences in DHE or dextran concentrations during single-dose administration (Figs. 1–4), nor was there any significant change in DHE concentrations in the multiple-dose study, despite the considerable increase in plasma volume produced by dextran. Trough levels of dextran on the other hand were increased when the combined therapy DHE/dextran 70 was given. One reason for this could be the effect of DHE on plasma volume. DHE increases central venous blood volume like total water immersion, thus activating the Gauer-Henry reflex, which induces a diuresis and a decrease in plasma volume (Gauer 1975). The differences between the single- and multiple-dose studies in this effect might have been because the first measurement of the trough level in the multiple-dose study was made 36 h after the initial injection of DHE, thus allowing time for changes in plasma volume to occur.

Acknowledgement. The dextran concentrations were kindly determined by P. Svensson and N. Bodin, Department of Biologic Analysis, Pharmacia AB, Uppsala, Sweden. The study was supported by grants from Swedish Research Council (00759).

References

- Åberg M, Arfors K-E, Bergentz S-E (1977) Effect of dextran on factor VIII and thrombus stability in humans. Significance of varying infusion rates. *Acta Chir Scand* 143: 417–419
- Aellig WH, Nüesch E (1977) Comparative pharmacokinetics investigations with tritium-labelled ergot alkaloids after oral and intravenous administration in man. *Int J Clin Pharmacol* 15: 106–112
- Bergqvist D, Efsing HO, Hallböök T, Lindblad B (1980) Preven-

- tion of postoperative thromboembolic complications. A prospective comparison between dextran 70, dihydroergotamine heparin and a sulphated polysaccharid. *Acta Chir Scand* 146: 559–568
- Bobik A, Skews H, Jennings G, Esler M, Korner PI (1980) Dihydroergotamine kinetics in patients with orthostatic hypotension. *Clin Exp Pharmacol Physiol* 7: 684
- Buttermann G, Theisinger W, Oechsler H, Hör G (1975) Untersuchungen über die postoperative Thromboembolie-Prophylaxe nach einem neuen medikamentösen Behandlungsprinzip. *Dtsch Med Wochenschr* 100: 2065–2069
- Gauer OH (1976) Moderator's introduction. *Cardiology* 61: [Suppl 1] 2–6
- Hilke H, Kanto J, Mäntylä R, Kleimala T, Syvälahti E (1978) Dihydroergotamine: Pharmacokinetics and usefulness in spinal anaesthesia. *Acta Anaesthesiol Scand* 22: 215–220
- Jenner H (1967) Automated determination of the molecular weight distribution of dextran. 3rd European Technicon Symposium Brighton, England, p203–207
- Kunz S, Drähne A, Briel RC (1977) Prophylaxe der postoperativen Thromboembolie-Erfahrungen mit Heparin Dihydergot® in der Gynäkologie. In: Pabst HW, Maurer G (ed) Postoperative Thromboembolie-Prophylaxe. 6. Rothenburger Gespräch 20–21 Mai 1977. Schattauer, Stuttgart, pp 134–144
- Lamke LO, Liljedahl SO (1976) Plasma volume changes after infusion of various plasma expanders. *Resuscitation* 5: 93–106
- Lange LM, Echt M (1972) Vergleichende Untersuchungen über venentonisierende Pharmaka. *Fortschr Med* 90: 1161–1173
- Little PJ, Jennings GL, Skews H, Bobik A (1982) Bioavailability of dihydroergotamine in man. *Br J Clin Pharmacol* 13: 785–790
- Meier J, Schreier E (1976) Human plasma levels of some anti-migraine drugs. *Headache* 16: 96–104
- Mühe E, Burghardt K-H, Kolb W, Strobel G (1975) Eine neue Methode zur Prophylaxe postoperativer Venenthrombosen. *Klinikarzt* 4: 88–92
- Müller-Schweinitzer E (1980) In vitro studies on the duration of action of dihydroergotamine. *Int J Clin Pharmacol Ther Toxicol* 18: 88–91
- Olver I, Jennings G, Bobik A, Esler M (1980) Low bioavailability as a cause of apparent failure of dihydroergotamine in orthostatic hypotension. *Br Med J* 2: 275–276
- Rosenthaler J, Munzer H (1976) 9,10-Dihydroergotamine: Production of antibodies and radioimmunoassay. *Experientia (Basel)* 32: 234–236
- Sagar S, Stamatakis JD, Higgins AF, Nairn D, Maffei FH, Thomas DP, Kakkar VV (1976) Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total hip replacement. *Lancet* 2: 1151–1154
- Sheiner LB (1981) ELSFIT. A program for the extended least squares FIT to individual pharmacokinetic data. Users manual. A technical report of the Division of Clinical Pharmacology of California, SF, CA 94143
- Stamatakis JD, Sagar S, Lawrence D, Kakkar VV (1977) Dihydroergotamine in the prevention of postoperative deep venous thrombosis. *Br J Surg* 64: 294
- Thorén L (1978) Dextran as a plasma volume substitute. *Progr Clin Biol Res* 19: 265–282

Received: November 3, 1982

in revised form: February 19, 1983

accepted: March 4, 1983

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THE EFFECT OF DIHYDROERGOTAMINE ON PLATELETS, COAGULATION AND FIBRINOLYSIS, STUDIED IN HEALTHY HUMANS AND IN DOGS

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ABSTRACT

The effect of dihydroergotamine (DHE) on platelets, coagulation and fibrinolysis was studied in healthy volunteers ex vivo before and after intravenous administration (0.5 mg). In addition, the effect of DHE in different concentrations on platelet aggregation was evaluated in vitro. Haematocrit was found to increase, as did factor VIII:C and antithrombin III - though the latter increases were not significant when correction was made for the altered haematocrit. Though platelet function ex vivo was unchanged, inhibition of adrenaline induced platelet aggregation was noted in vitro when the plasma concentrations of added DHE were higher than those obtained with clinically relevant doses. No effect on fibrinolysis was noted.

INTRODUCTION

Dihydroergotamine (DHE) effectively reduces postoperative venous thromboembolism, especially in combination with low dose heparin (1, 2), this effect being said to be due to effects on peripheral haemodynamics. DHE increases tonus mainly in capacitance vessels, reducing blood pooling (3), and increasing the rate of venous blood flow (4). Some reports have indicated that platelet function is affected by DHE (5,6). This study was done to establish further data on the effects of DHE on platelets, and on coagulation and fibrinolysis.

Key words: Thromboembolic prophylaxis, dihydroergotamine, platelet function, coagulation, fibrinolysis

MATERIAL AND METHODS

Where not otherwise stated, blood samples were drawn from an antecubital vein. Whole blood, serum, citrated platelet poor and platelet rich plasma were prepared as previously described (7).

A solution of DHE, (dihydroergotamine methanesulphonate, Orsta-norm[®], Sandoz AB, Täby, Sweden) at a concentration of 1 mg/ml was used. The study was approved by the Medical Ethics Committee, University of Lund, and all volunteers gave their informed consent.

Platelet aggregation in vitro:

Platelet rich plasma was prepared from 8 healthy volunteers (4 females, 4 males; median age 33, range 24-42 years). No pharmacotherapy was allowed for two weeks before the investigation. Platelet aggregation studies were performed according to Born (8). An aggregometer (Payton dual channel) connected to a writer (Linear) was used and light transmission was calibrated before measurements were made. To 450 μ l platelet rich plasma, various dilutions of DHE (50 μ l) were added, giving final concentrations between $1 \cdot 10^{-1}$ g/l to $1 \cdot 10^{-8}$ g/l of DHE. After different incubation times of DHE (one, two or three minutes), aggregation was induced either by 50 μ l of adrenaline ($5 \cdot 10^{-4}$ M), ADP ($5 \cdot 10^{-5}$ M), collagen (100 μ g/ml), or serotonin (1 mg/ml) one minute before adding either adrenaline, ADP or collagen.

50 μ l isotonic saline being added to reference samples instead of DHE, the following evaluations were made: the maximal slope of the first wave in the aggregation, expressed in mm/min; the existence, or not, of a second slope; and the change in light transmission five minutes after the induction of aggregation, expressed in percent.

Study of healthy volunteers:

Ten healthy volunteers (6 males, 4 females) with a median age of 30 years (range 21-41), and bodyweight of 52-92 kg (median, males 73 kg; median, females 57 kg) were studied. No pharmacotherapy was allowed for two weeks before the study. Blood samples and vein biopsies were taken prior to and 30 min after administration of 0.5 mg DHE i.v.

Haemoglobin content, haematocrit, leucocytes and C-reactive protein were determined.

Platelet tests: Assays were made of the platelet count (9), platelet factor 3 (10) (amidolytically), and of platelet adhesiveness according to Hellem (11) as modified by Cronberg et al., (12). Studies were also made of platelet aggregation according to Born (8), platelet aggregation being induced with the following: adrenaline, ADP, and collagen, and each of them in combination with serotonin.

Coagulation and fibrinolytic tests: As previously described (7), Owren's P&P method (prothrombin + factor VII + factor X) was performed, and the following determined: factors V, VIII:C and VIII:R Ag; fibrinogen, fibrin/fibrinogen degradation products

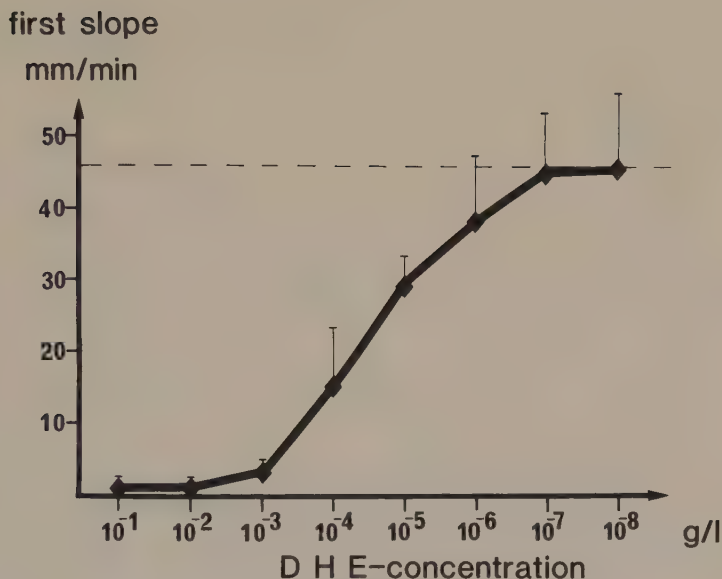


FIG. 1

Changes in maximal slope in adrenaline induced platelet aggregation in vitro after adding DHE in different concentrations. The dotted line represents the slope for adrenaline induced platelet aggregation when saline instead of DHE was added (mean $\pm$ SEM).

(FDP), and inhibitors of plasminogen activation; and recalcification time, activated partial thromboplastin time (APTT), one stage prothrombin time, and euglobulin clot lysis time. Antithrombin III (AT III) and α_2 -antiplasmin (α_2 AP) were assayed both amidolytically (S-2238, S-2251), and immunochemically using Laurell's rocket technique (13). α_2 -macroglobulin (α_2 M) was measured esterolytically according to Granrot (14). The fibrinolytic activity of plasma and resuspended euglobulin precipitate was measured on fibrin plates according to Nilsson and Olow (15), and the plasminogen activator activity in the vessel wall determined histologically according to Pandolfi (16).

Experimental studies:

In six dogs weighing between 15 and 20 kg anaesthetized with phenobarbital, DHE in a dose of 0.01 mg/kg body weight was given intravenously. Dextran 70 0.5 g/kg (Macrodex 6% in NaCl, Pharmacia, Sweden) was given to two dogs simultaneously. Blood samples were taken from a peripheral vein, the pulmonary artery, left atrium and aorta. Fibrinogen, FDP, fibrinolytic activity of cit-

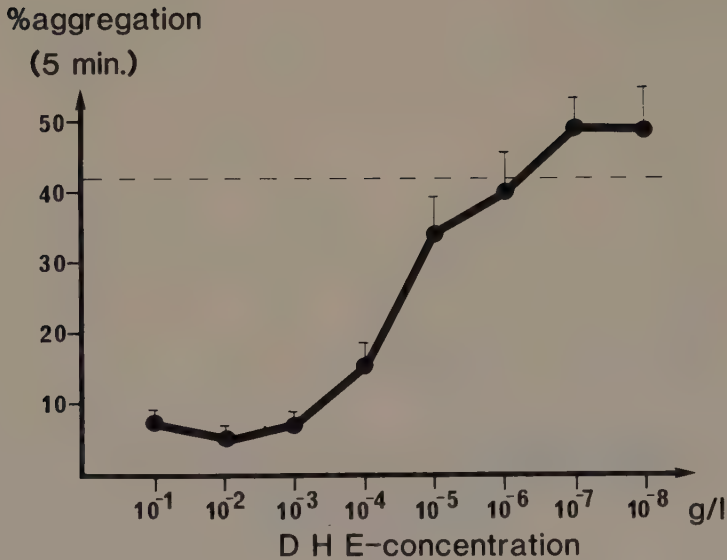


FIG. 2

Change (%) in platelet aggregation in vitro five minutes after induction with adrenaline after preincubation (1 min) with various concentrations of DHE. The dotted line represents the change in aggregation when 50 μ l NaCl instead of DHE was given (mean $\pm$ SEM).

rate plasma on fibrin plates and euglobulin clot lysis time were observed as well as haemoglobin, haematocrit and blood gases. Blood samples for measurements were taken before the drug administration and 15 min after.

Statistics:

Statistical analysis was made using the Student t-test for paired data where distribution was normal and Wilcoxon rank sum test elsewhere. The level of significance was chosen as $p < 0.05$.

RESULTS

In the in vitro experiments DHE in concentrations of $1 \cdot 10^{-4}$ g/l or higher was found to affect platelet aggregation induced by adrelanine, as seen by the reduced maximal slope of the first wave (Fig. 1), and the absence of a second wave. When the concen-

TABLE I

Blood variables after DHE in healthy volunteers (n=10, mean value $\pm$ SEM) (* = $p < 0.05$, ** = $p < 0.01$).

		<u>Before</u>	<u>After 0.5 mg DHE i.v.</u>
Hemoglobin	g/l	143 $\pm$ 4	147 $\pm$ 4*
EVF	%	42 $\pm$ 1	44 $\pm$ 1**
Leucocytes	10^9 /l	7330 $\pm$ 795	7210 $\pm$ 760
C-reactive protein	mg/l	0	0

TABLE II

Effects on platelet aggregation by DHE in healthy volunteers (n = 10, mean value $\pm$ SEM).

	<u>Before</u>		<u>After 0.5 mg DHE i.v.</u>	
	Max slope (mm/min)	% aggr 5 min	Max slope (mm/min)	% aggr 5 min
ADP	99 $\pm$ 10	41 $\pm$ 5	108 $\pm$ 7	43 $\pm$ 4
ADP + serotonin	88 $\pm$ 8	37 $\pm$ 4	97 $\pm$ 8	36 $\pm$ 3
Collagen	145 $\pm$ 16	56 $\pm$ 2	154 $\pm$ 15	55 $\pm$ 2
Coll. + serotonin	109 $\pm$ 9	53 $\pm$ 2	95 $\pm$ 11	53 $\pm$ 2
Adrenaline	47 $\pm$ 6	49 $\pm$ 4	42 $\pm$ 5	45 $\pm$ 5
Adren. + serotonin	57 $\pm$ 7	43 $\pm$ 6	43 $\pm$ 5	39 $\pm$ 5

TABLE III

Effects on coagulation by DHE in healthy volunteers
(n = 10, mean value $\pm$ SEM) (* = $p < 0.05$).

		Before	After 0.5 mg DHE i.v.
Recalcification time	s.	145 $\pm$ 9	137 $\pm$ 10
APT time	s.	29 $\pm$ 1	29 $\pm$ 1
Thromboplastin time	s.	15.3 $\pm$ 0.3	15.3 $\pm$ 0.3
Owren's P&P	%	116 $\pm$ 5	116 $\pm$ 6
Factor VIII:C	%	144 $\pm$ 7	163 $\pm$ 12*
Factor VIII:R Ag	%	125 $\pm$ 8	136 $\pm$ 8
Factor V	%	105 $\pm$ 6	111 $\pm$ 9
Antithrombin III (imm.)	%	101 $\pm$ 4	104 $\pm$ 3
-"- (S-2238)	%	108 $\pm$ 3	114 $\pm$ 3*

tration was lower, a second wave was seen and the magnitude of the maximal slope normalized. The change in light transmission five minutes after adding adrenaline was successively inhibited reaching statistically significant values at DHE concentrations $1 \cdot 10^{-5}$ g/l or higher (Fig. 2). Serotonin-adrenaline induced aggregation showed similar results. The pre-incubation time of DHE - one, two or three minutes - did not affect on the results. ADP and collagen induced aggregation, even when combined with serotonin, was unaffected by DHE.

In the ex vivo experiments on healthy volunteers, haemoglobin content and haematocrit increased (Table I). After 0.5 mg DHE intravenously, platelet count was unchanged (267 $\pm$ 23 resp. 270 $\pm$ 23 10^9 g/l), as was platelet factor 3 (PF₃, 145 $\pm$ 12 resp. 135 $\pm$ 14%). Platelet adhesiveness was slightly reduced ($p < 0.05$, 23.4 $\pm$ 1.2 resp. 21.2 $\pm$ 1.5%). No significant effect on platelet aggregation was found (Table II). Coagulation variables were largely unaffected (Table III). Slight increase in Factor VIII:C and antithrombin III were noted (when measured amidolytically). These were due to altered haematocrit since after correction for its alteration no change was seen. Fibrinolysis was unchanged (Table IV).

In the dogs no fibrinolytic activation was seen after administration of DHE. Fibrinolysis remained unchanged, in both systemic and pulmonary circulation, after DHE administration.

TABLE IV

Effects on fibrinolysis by DHE in healthy volunteers (n = 10, mean value $\pm$ SEM).

		Before	After 0.5 mg DHE i.v.
Fibrinogen	g/l	3.2 $\pm$ 0.2	3.2 $\pm$ 0.2
FDP	mg/l	0	0
Fibrinolytic activity on fibrin plates:			
citrated plasma	mm ²	14.9 $\pm$ 6.6	16.2 $\pm$ 6.2
euglobulin precipitate	mm ²	196 $\pm$ 16	228 $\pm$ 21
Euglobulin clot lysis time	min	164 $\pm$ 17	160 $\pm$ 23
Plasminogen	%	107 $\pm$ 5	113 $\pm$ 7
Inhibitor of the activa- tion of plasminogen	%	104 $\pm$ 4	107 $\pm$ 6
α_2 -macroglobulin	%	94 $\pm$ 8	94 $\pm$ 7
α_2 -antiplasmin (imm.)	%	101 $\pm$ 5	104 $\pm$ 7
α_2 -antiplasmin (S-2251)	%	108 $\pm$ 3	105 $\pm$ 2
Plasminogen activator activity in vein biopsies (median value and range)	arb. units	6.75 (5.50-8.75)	7.0 (4.25-10.50)

DISCUSSION

It has previously been shown that DHE competitively inhibits adrenaline and serotonin-adrenaline induced platelet aggregation on rabbit platelets in vitro, even when low concentrations of DHE were added (5). Our data on human platelets also shows that DHE affects platelet aggregation induced by adrenaline. However, no effect was noted when the concentration of DHE was low and comparable to plasma concentrations achieved by clinical dosages of DHE ($1 \cdot 10^{-6}$ - $1 \cdot 10^{-7}$ g/l). No effect on ADP or collagen induced in vitro platelet aggregation was seen. This is consistent with the ex vivo finding in healthy volunteers, where no effect on ADP, collagen, adrenaline or serotoninadrenaline induced platelet aggregation was found after administration of 0.5 mg DHE i.v. Nor does DHE in combination with low dose heparin influence collagen or adrenaline induced platelet aggregation ex vivo (17). Although significant, the decrease in platelet adhesiveness we found

is very small. Experimentally haemostatic platelet plug formation in the microvessels of the rabbit mesentery, and laser induced platelet microembolism in arterioles in rabbit ear chamber were largely unchanged after administration of DHE (18). To conclude, DHE in clinically relevant doses only affects platelet function to a minor extent.

In our healthy volunteers an increase in haemoglobin content and haematocrit was found after DHE administration. In earlier studies on cats and dogs a significant increase in haematocrit was also noted after DHE (19, 20). This could be due to plasma volume decrease.

We were unable to verify the increased, as compared with the predicted, post-operative antithrombin III concentrations reported in an uncontrolled study of patients undergoing surgery who had received DHE (21). Though it is well known that low antithrombin III values predispose to thrombosis development, high values have not, per se, been shown to counteract thrombus formation.

Release of plasminogen activators can be stimulated by various vasoactive substances (22). Though, since DHE increases vein tonus, it is theoretically possible that DHE could induce fibrinolytic activation, our findings with regard to fibrinolytic function disclosed no such effect. Vein wall biopsies showed no alteration in plasminogen activator activity.

Since pulmonary vessels are known to have high concentrations of plasminogen activators (22), and DHE increases pulmonary artery pressure (20), plasminogen activators might have been expected to be affected. In dogs, however, no release of fibrinolytic activity into the systemic or pulmonary circulation was found.

The fact that both factor VIII:R Ag, and the plasminogen activators released in parallel with it, remained unaffected by DHE indicates that endothelial release is not stimulated by DHE, despite its promoting increased vein tonus.

Plasmin has been said to interact with the balance of factor VIII:C and factor VIII:R Ag, resulting in increased mobility and falsely high values when measuring factor VIII:R Ag with the rocket technique (23). Our results do not, however, bear this out, as no major alteration in factor VIII:C was found.

To sum up, DHE seems to have no marked effect on platelets, coagulation, or fibrinolysis, when clinical dosages (0.5 mg i.v. or s.c.) are given. Haematocrit was found to have increased, probably due to plasma volume reduction. With our present knowledge, the thromboprophylactic action of DHE can only be accounted for by haemodynamic effects.

ACKNOWLEDGEMENTS

This study was supported by grants from Sandoz AB, Sweden, the Hulda Almroth and the Greta and Johan Kock foundations, research grants from the University of Lund, and the Swedish Research Council (Nos. 00759 and 05447). The skilful assistance of Inger Olsson and Elsy Sjörin has been greatly appreciated.

REFERENCES

1. BERGQVIST, D., EFSING, H.O., HALLBÖÖK, T. and LINDBLAD, B. Prevention of postoperative thromboembolic complications. A prospective comparison between dextran 70, dihydroergotamine heparin and a sulphated polysaccarid. Acta Chir. Scand. 146, 559-568, 1980.
2. GRUBER, U.F. Prevention of fatal postoperative pulmonary embolism by heparin dihydroergotamine or Dextran 70. Br. J. Surg. 69, 54-58, 1982.
3. MELLANDER, S. and NORDENFELT, I. Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. Cli. Sci. 39, 183-201, 1970.
4. RIECKERT, H. Primäre Therapieziele bei der hypotonen Fehlregulation. Fortschr. Med. 89, 175-176, 1971.
5. BARTHEL, W. and MARKWARDT, F. Aggregation of blood platelets by biogenic amines and its inhibition by antiadrenergic and antiserotonergic agents. Biochem. Pharmacol. 23, 37-45, 1974.
6. KAKKAR, V.V. Knowledge and prospective of thromboembolic research. In: Postoperative Thromboemboli-Prophylaxe aus aktueller Sicht. Eds.: Tscherne, H., Deutsch, E. Georg Thieme Verlag, Stuttgart, New York. pp. 1-6, 1981.
7. NILSSON, I.M. Haemorrhagic and thrombotic diseases. Wiley and Sons Ltd., London. 1974.
8. BORN, G.V.R. Aggregation of blood platelets by adenosine diphosphate and its reversal. Nature 194, 927-929, 1962.
9. BJÖRKMAN, S.E. A new method for enumeration of platelets. Acta Haematol. 22, 377-379, 1959.
10. SANDBERG, H., GELLERBRING, A.K. and ANDERSSON, L.O. Determination of platelet factor 3 in whole blood by a chromogenic peptide substrate assay. Thromb. Res. 18, 871-882, 1980.
11. HELLEM, A.J. The adhesiveness of human platelets in vitro. Scand. J. Clin. Lab. Invest. 12, 1-117, 1960.
12. CRONBERG, S., NILSSON, I.M. and SILVER, J. Studies on the platelet adhesiveness in von Willebrand's disease. Acta Med. Scand. 180, 43-54, 1966.
13. LAURELL, C.-B. Quantitative estimation of proteins by electrophoresis in agarose gel containing antibodies. Anal. Biochem. 15, 45-52, 1966.

14. GANROT, P.O. Determination of α_2 -macroglobulin as trypsin-protein esterase. Clin. Chim. Acta 14, 493-501, 1966.
15. NILSSON, I.M. and OLOW, B. Determination of fibrinogen and fibrinogenolytic activity. Thrombos. Diathes. Haemorrh. 8, 297-310, 1962.
16. PANDOLFI, M., BJERNSTAD, A., and NILSSON, I.M. Technical remarks on the microscopical demonstration of tissue plasminogen activator. Thrombos. Diathes. Haemorrh. 27, 88-98, 1972.
17. VINAZZER, H. Gerinnungsparameter unter Low-Dose Heparin und Heparin-DHE. In: Postoperative Thromboembolie-Prophylaxe aus aktueller Sicht. Eds: Tscherne, H., Deutsch, E. Georg Thieme Verlag, Stuttgart, New York. pp. 108-110, 1981.
18. BERGQVIST, D., ARVIDSSON, S., ESQUIVEL, C.O., HAGLUND, U. and LINDBLAD, B. The effect of serotonin inhibition on initial microvessel haemostasis and platelet aggregation in vivo. Thrombos. Haemost. In press.
19. ARFVIDSSON, S., LINDBLAD, B., ESQUIVEL, C.O., BERGQVIST, D. and HAGLUND, U. Haemodynamic effects of dihydroergotamine and ketanserin in E. coli bacteremic chock. Scand. J. Clin. Lab. Invest. In press.
20. LINDBLAD, B. and BERGQVIST, D. Central hemodynamic effects of dextran 70, dihydroergotamine and their combination. A study in dogs. Acta Chir. Scand. In press.
21. SVANBERG, L., BERNSTEIN, K., KULLANDER, S. and ÅSTEDT, B. Effects of dihydroergotamine on coagulation factors and components of the fibrinolytic system. Acta Obstet. Gynec. Scand. 59, 251-253, 1980.
22. CASH, J.D. Neurohumoral pathways associated with the release of plasminogen activator in man. In: Progress in Chemical Fibrinolysis and Thrombolysis. Eds: Davidson, J.F., Samama, M., Desnoyers, P.C. New York, Raven Press. 1, 97-107, 1975.
23. HENRIKSSON, P. and HOLMBERG, L. Factor VIII activity and antigen in sick newborns with pathological proteolysis in blood. Acta Paediatr. Scand. 67, 83-87, 1978.

DOES DIHYDROERGOTAMINE POTENTIATE THE THROMBOPROPHYLACTIC EFFECT OF DEXTRAN 70? A CONTROLLED PROSPECTIVE STUDY IN GENERAL AND HIP SURGERY.

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ABSTRACT

In a prospective randomized controlled study on postoperative thromboembolism 259 patients undergoing elective general surgery, emergency general surgery, total hip replacement or hip fracture surgery were given thromboembolic prophylaxis with either a combination of dextran 70 and dihydroergotamine (DHE) or with dextran 70 alone. 500 ml dextran 70 was infused twice on the operation day, once on postoperative days 1 and 3, and also on day 5 if the patient was still confined to bed. 0.5 mg DHE was given s.c. twice daily starting before operation and continued for 3 or 5 postoperative days as above. In hip fracture patients prophylaxis was started as soon as the diagnosis was made, 500 ml dextran 70 was given every other day before operation, DHE was given twice daily if so indicated from randomization. The patients were screened for deep-vein thrombosis (DVT) with the ¹²⁵I-fibrinogen test for 8 days and followed for one month postoperatively. In hip fracture surgery the incidence of DVT was significantly reduced by the combination of dextran 70 and DHE compared to dextran 70 alone (1/32 vs. 11/36, $p=0.003$). However, this synergistic effect of DHE could not be detected in the other patient categories. Fatal pulmonary embolism did not occur. No severe side effects attributable to prophylaxis were noted in either group.

Key words: Dextrans, dihydroergotamine, hip fractures, thrombosis.

INTRODUCTION

Dextran was first used for the prophylaxis of postoperative thromboembolism over 20 years ago (1), and has been found particularly effective in high risk groups, such as patients with hip fractures (2,3). Dihydroergotamine (DHE) has in recent years also been shown to have a thromboprophylactic effect (4), but above all to have a synergistic effect together with low-dose heparin in prophylaxis of deep-vein thrombosis (DVT) (5). In hip fracture patients this synergism is not as clear (6, 7).

DHE increases the tone in capacitance vessels, thus increasing venous blood flow velocity (8,9). Dextran modifies thrombus structure (10) and causes haemodilution, which should make a synergistic effect of the two substances possible.

The aim of this study was therefore to investigate if the addition of DHE increases the efficacy of dextran 70 in the prophylaxis of postoperative thromboembolism after elective and emergency general surgery, total hip replacement and hip fracture operations.

PATIENTS AND METHODS

The study was performed January 1981 - December 1982 at three centers: Kärnsjukhuset, Skövde; Allmänna Sjukhuset, Malmö and Danderyds Sjukhus, Danderyd. A total of 318 patients were admitted to the study. Four categories of patients were studied: elective general surgery, emergency general surgery, total hip replacement (THR) and acute hip fracture surgery. Each category was separately randomized as to prophylactic method using numbered sealed envelopes. The number of patients in each category was calculated from previous incidence figures for DVT to give possibility of detecting a clinically interesting difference. Patients could be admitted if they were over the age of 50 and in the cases of elective and emergency general surgery when operation time was calculated to be half an hour or more. The

Table I

Reasons for exclusions.

29 patients with dextran 70 and 30 patients with dextran 70 + DHE prophylaxis were excluded.

DHE	Dextran 70	Dextran 70 +
	(number of patients excluded)	
<u>Elective general surgery</u>		
Incomplete fibrinogen test	0	1
Incorrect prophylaxis	0	1
Total	0	2
<u>Emergency general surgery</u>		
Incomplete fibrinogen test	8	5
Incorrect prophylaxis	1	6*
Total	9	11
<u>Total hip replacement</u>		
Incomplete fibrinogen test	2	0
Operation postponed	1	0
Total	3	0
<u>Hip fracture surgery</u>		
Incomplete fibrinogen test	3	0
Incorrect prophylaxis	2	3
Operation postponed	0	3
Hip fracture operated according to Ender (fibrinogen test inconclusive)	12	11
Total	17	17
TOTAL	29	30

*5 of these 6 patients were screened for DVT with negative results.

Table II

Age, weight, sex, operation time, side of operation and frequency of epidural and spinal anaesthesia. Results given as median and range unless otherwise stated.

Prophylaxis	No. of pat.	Age (years)	Weight (kg)	Sex (% fe- males)	Opera- tion time (min.)	Side of operation (no. right/ no. left)	Epidura or spin anaesth esia (%)
<u>Elective general</u> <u>surgery</u>							
Dextran 70	28	66 (50-81)	66 (47-90)	54	85 (35-230)		11
Dextran 70 + DHE	31	68 (54-88)	65 (50-118)	35	75 (15-165)		16
<u>Emergency general</u> <u>surgery</u>							
Dextran 70	31	69 (53-91)	66 (49-94)	52	83 (31-200)		3
Dextran 70 + DHE	20	67 (50-83)	66 (48-85)	45	82 (25-220)		5
<u>Total hip</u> <u>replacement</u>							
Dextran 70	41	68 (50-85)	76 (57-112)	41	92 (45-205)	24/17	83
Dextran 70 + DHE	40	68 (55-80)	73 (46-95)	48	83 (50-160)	20/20	78
<u>Hip fracture</u> <u>surgery</u>							
Dextran 70	36	74 (51-93)	60 (45-75)	69	28 (10-85)	13/23	67
Dextran 70 + DHE	32	79 (54-96)	52 (46-76)	78	26 (10-115)	13/19	63

Table III

Risk factors.

Number of patients.

	No. of pat.	Obesity (Broca's index 1.25)	Varicose veins and related disorders	Malignancy	Cardiovascular or pulmonary disorders	Previous thrombo-embolic disease	Average no. of risk factors/patient.
<u>Elective general surgery</u>							
Dextran 70	28	1	17	8	12	3	1.5
Dextran 70 + DHE	31	5	13	9	5	3	1.1
<u>Emergency general surgery</u>							
Dextran 70	31	1	16	7	6	2	1.0
Dextran 70 + DHE	20	1	9	3	6	3	1.1
<u>Total hip replacement</u>							
Dextran 70	41	2	25	0	15	6	1.2
Dextran 70 + DHE	40	4	26	1	15	7	1.3
<u>Hip fracture surgery</u>							
Dextran 70	36	0	12	2	15	3	0.9
Dextran 70 + DHE	32	0	9	2	20	1	1.0

following types of patients were not admitted to the study: patients undergoing thoracic, breast, endocrine or vascular surgery; patients with hypersensitivity to iodine, dextran or DHE; patients with thyroid diseases; patients with haemorrhagic diseases; patients receiving therapy with anti-coagulants or having taken aspirin or other anti-platelet drugs during the 5 days preceding the operation. Both general and regional (spinal and epidural) anaesthesia was used, but DHE was not allowed to be used during regional anaesthesia for prophylaxis of hypotension. All patients undergoing elective surgery were fully mobile before operation.

Patients with incomplete fibrinogen tests or who could not continue the full course of prophylaxis due to factors unrelated to prophylaxis were excluded, Table I. The age, weight, sex, operation time and frequency of regional anaesthesia are shown in Table II. In hip surgery the side of operation is also shown. Table III shows risk factors apart from age over 50. The types of operations and number of malignancies (general surgery) are shown in Table IV.

The study was approved by ethical committees and informed consent was obtained from all patients before they entered the study.

Prophylactic methods.

The patients were randomized to receive thromboembolic prophylaxis with either dextran 70 alone or a combination of dextran 70 and DHE. Physiotherapy was given routinely, and all patients (including those with hip operations) were usually mobilized on the first postoperative day.

1. Dextran prophylaxis. 500 ml dextran 70 (Macrodex^R, 6 % in saline, Pharmacia AB, Uppsala, Sweden) was given during operation, another 500 ml postoperatively on the same day, and 500 ml on the first and third postoperative days. Patients still confined to bed at this stage were also given 500 ml on the fifth postoperative day. Infusion time was 2-4 hours. Twelve patients weighing less than 50 kg were given 250 ml dextran 70 on all occasions except during operation. All patients were given 20 ml dextran 1 (Promiten^R, Pharmacia AB, Uppsala, Sweden) i.v. before the first infusion of dextran 70 for the prevention of anaphylactic reactions to dextran (11,12).

2. DHE prophylaxis. 0.5 mg dihydroergotamine methanesulfonate (Orstanorm^R, Sandoz AB, Täby, Sweden) was given subcutaneously on the lateral aspect of the thigh twice daily, starting on the evening before operation in elective surgery and with premedication in emergency surgery. DHE was given for three days postoperatively, and continued for another two days if the patient was still confined to bed.

In hip fracture patients prophylaxis was started as soon as diagnosis was made after arrival at the hospital. Dextran 70 was given every other day until operation and DHE was given twice daily if so indicated from randomization. During operation and afterwards the prophylaxis was given as in the other categories.

Hip surgery techniques.

All THR procedures were performed through a posterolateral incision without osteotomy of the greater trochanter. Charnley, Brunswick and Stanmore prostheses were used. Hip fractures were nailed using pin (Thorn-ton or Rydell) or pin + plate (Pugh). No hip fracture was operated with prosthesis.

Diagnostic methods.

The development of DVT was screened with the ¹²⁵I-fibrinogen test. External scanning using a scintillation counter with a scaler was performed according to Kakkar et al. (13) with slight modifications (14). Both legs were scanned at eight different points at least every second day during the first eight postoperative days. Scanning was started preoperatively in all elective patients. If the fibrinogen test became positive, scanning was performed daily. Each patient scheduled for elective surgery received 100 microcurie ¹²⁵I-labelled fibrinogen (Amersham, England) iv on the day before operation. Patients with hip fractures were injected as soon as scanning could begin, always before surgery. Patients undergoing emergency general surgery were injected as soon as scanning could begin, usually after surgery. If necessary, the ¹²⁵I-fibrinogen dose was repeated once. The thyroid was blocked before the isotope injection with either oral KI 150-200 mg or i.v. NaI 150 mg and continued thereafter for 10 days.

The criterion for diagnosis of DVT at a certain point was a difference in counts of 20% or more from an adjacent point on the same leg or at the same position on the opposite leg. The difference should persist or increase during the next 24 hours. If possible, phlebography was performed for confirmation.

All patients were followed 30 days after operation. Six patients died during this period, and autopsy was performed in four of these cases.

Complications.

Peroperative bleeding was estimated from the content of blood in swabs and from measurement of blood in suction bottles. Transfusion requirements were calculated from the need during and after surgery. One unit of blood is equivalent to 400 ml whole blood or 200 ml erythrocyte concentrate. All patients with bleeding complications requiring surgical intervention (reoperation, debridement) were noted. Infectious complications, cardiac overload, allergy or other complications that could be attributable to prophylaxis were noted on the patients' proformas.

Statistical methods.

Wilcoxon's rank sum test, Fisher's exact test and Chi-square test with Yates' correction were used for the statistical analyses. P-values greater than 0.05 were regarded as non-significant (n.s.).

RESULTS

The two prophylaxis groups were well matched for all factors studied in each of the four categories of surgery (Table II-IV). Pertrochanteric fractures constituted 19% of the hip fractures in the dextran 70 group and 16% in the combination group. In hip fracture patients the median time between admission and operation was 1.5 and 1.8 days, respectively.

A total of 48 of the 259 patients studied were diagnosed as having developed DVT, Table V. Three of these patients had bilateral DVT. The DVT were diagnosed after the fifth post-operative day in seven patients. No elective patient showed signs of DVT on the preoperative scanning. Phlebography performed in 20 patients confirmed the fibrinogen test in 16 of these.

Table IV

Type of operation and number of malignancies in
elective and emergency general surgery.
Number of malignancies within brackets.

	Elective general surgery		Emergency general surgery	
	Dextran 70	Dextran 70+DHE	Dextran 70	Dextran 70+DHE
Gastric surgery	2 (1)	3 (2)	5 (1)	4
Biliary surgery	12	9	9	7
Colon surgery	8 (7)	8 (7)	5 (5)	2 (2)
Explorative laparotomy	0	2	0	0
Nephrectomy and stone operations	4	2	0	0
Prostatectomies	2	7	0	0
Intestinal obstruction	0	0	8 (1)	5 (1)
Miscellaneous	0	0	4	2

Table V

Incidence of DVT in different patient categories after thromboembolic
prophylaxis with dextran 70 or dextran 70 + DHE.
Results given as no. of patients with DVT/total no. of patients.

Patient category	Dextran 70		Dextran 70 + DHE
Elective general surgery	1/28	n.s.	4/31
Emergency general surgery	4/31	n.s.	2/20
Total hip replacement	10/41	n.s.	15/40
Hip fracture surgery	11/36	p=0.003	1/32

Table VI
Causes of death in six patients dying
within one month after operation.

	Age	Sex	Postop. day	Prophylaxis
<u>Elective general surgery</u>				
1. Anterior resection of rectal cancer; anastomotic leakage with peritonitis.	81	F	11	Dextran 70
2. Exploratory laparotomy for suspected colon cancer; bilateral pneumonia and myocardial infarction.	88	M	7	Dextran 70 + DHE
3. Gastric resection for ulcer; delayed rupture of subcapsular splenic hematoma, death during induction of anaesthesia for reoperation.	58	M	3	Dextran 70 + DHE
<u>Emergency general surgery</u>				
4. Perforated gastric ulcer; myocardial infarction and pulmonary oedema.	82	F	2	Dextran 70 + DHE
<u>Hip fracture surgery</u>				
5. Decompensated heart failure, pulmonary oedema (no autopsy)	89	F	3	Dextran 70
6. Decompensated heart failure, pulmonary oedema (no autopsy)	92	F	29	Dextran 70 + DHE

Table VIII
The incidence and location of DVT after total
hip replacement and hip fracture surgery.

	<u>Total hip replacement</u>		<u>Hip fracture operation</u>	
	Dextran 70	Dextran 70 + DHE	Dextran 70	Dextran 70 + DHE
Total no. of patients	41	40	36	32
DVT	10	15	11	1
Thigh thrombi	1	2	4	0
Thrombi in operated leg	7	13	9	1
Bilateral thrombi	1	1	0	0

Table VII

Peroperative bleeding and transfusion requirements.

	Peroperative bleeding (ml; median and range)	No. of pati- ents trans- fused.	Transfusion require- ments (units of blood median and range)
<u>Elective general surgery</u>			
Dextran 70	249 (35-1000)	5	1.9 (1-3)
Dextran 70 + DHE	303 (50-4000)	9	3.6 (2-9)
<u>Emergency general surgery</u>			
Dextran 70	261 (100-1000)	6	1.1 (1-2)
Dextran 70 + DHE	169 (25-800)	4	2.2 (1-4)
<u>Total hip replacement</u>			
Dextran 70	545 (150-2100)	28	2.7 (1-7)
Dextran 70 + DHE	540 (200-1800)	28	2.8 (1-8)
<u>Hip fracture surgery</u>			
Dextran 70	122 (20-700)	9	1.9 (1-4)
Dextran 70 + DHE	73 (5-500)	5	2.0 (2)

Elective general surgery.

DVT was diagnosed in one of 28 patients receiving dextran 70 and in four of 32 receiving dextran 70 + DHE (n.s.). One of the latter had a thigh thrombus, the others had only calf thrombi. Three patients died, Table VI. The peroperative bleeding and the transfusion requirements did not differ between the groups, Table VII. Five patients in the dextran 70 + DHE group received 4 to 9 units of blood, but this was in each case due to surgical complications unrelated to prophylaxis. Surgical complications also account for three reoperations for haemorrhage and two wound haematomas in this group, as compared to no such complications in the

dextran 70 group. A surgical complication was also the cause of death in one patient as seen from Table VI.

Emergency general surgery.

DVT was diagnosed in four of 31 patients receiving dextran 70 and in two of 20 receiving dextran 70 + DHE (n.s.). Two patients in the dextran 70 group had thigh thrombi, and one of them also had a calf thrombus in the other leg. One patient in the combination group possibly had a thigh thrombus (positive fibrinogen test but negative phlebography). The other patients only had calf thrombi. When comparing peroperative bleeding and transfusion requirements no significant differences were seen, Table VII. One patient in the combination group died, Table VI.

Total hip replacement.

The incidences of DVT in the two prophylaxis groups did not differ significantly, nor did the incidences of thigh thrombi, bilateral thrombi or thrombi in the operated leg, Table VIII. One calf vein thrombus was not confirmed by phlebography in a dextran treated patient. No mortality was observed after THR. There was no difference in bleeding or transfusion requirements between the two prophylaxis groups, Table VII. The only haemorrhagic complication was wound haematoma that had to be debrided in one patient in the dextran 70 group.

Hip fracture surgery.

The incidence of DVT was lower after prophylaxis with dextran 70 + DHE (one DVT in 32 patients, 3%) than after prophylaxis with dextran 70 alone (11 DVT in 36 patients, 31%), $p=0.003$, Table VIII. The incidences of thigh thrombi or bilateral thrombi were not significantly different. Two patients died, one in each group. Autopsy was not performed, and the clinically diagnosed causes of death are shown in Table VI. As in the previous categories no significant difference as to bleeding tendency could be detected after the two types of prophylaxis, Table VII. In one patient in each group evaluation of FUT was disturbed by haematoma in the thigh after nailing of a pertrochanteric fracture. In both patients phlebography excluded the presence of a thigh thrombus.

Side effects.

No patient given DHE showed any signs of impaired arterial circulation. One patient given DHE died from a myocardial infarction, Table VI. In patient no. 2 in this table the myocardial infarction was not diagnosed before death, which occurred several days after prophylaxis was finished. Two hip fracture patients, one in each of the prophylaxis groups, suffered nonfatal myocardial infarction. The patient receiving dextran 70 developed DVT, whereas the other patient whose DHE medication was interrupted did not.

Pulmonary oedema was diagnosed before death in two hip fracture patients, Table VI. In one patient death occurred more than three weeks after the last infusion of dextran. The other patient had signs of decompensated heart failure on admission, and was given a reduced dose of dextran, and no dextran infusion was given during the two days before death. In the patient with perforated ulcer in the same table, pulmonary oedema was secondary to myocardial infarction, and again no dextran was given during the last two days before death.

In four of 123 patients given DHE the prophylaxis had to be interrupted because of nausea possibly related to the DHE injections.

No allergic or anaphylactic reactions to dextran or DHE were observed.

DISCUSSION

DHE increases the tone of the capacitance vessels, thereby increasing the venous blood flow velocity (8,9). DHE may also alter peripheral resistance, an effect dependent on the sympathetic tone (15,16). In some studies the addition of DHE has been found to increase the concentration of heparin in plasma (17,18), but these results have not been confirmed by others (19,20). The concentration of dextran was also increased by the addition of DHE (21). Finally, DHE reduces platelet aggregation in vitro (22), but this effect is of uncertain significance in vivo and coagulation and fibrinolysis are not influenced (23). It is thus not clear how DHE increases the potency of antithrombotic agents such as low-dose heparin or dextran.

A great number of studies have shown hip fracture surgery to be associated with a high risk of DVT and pulmonary embolism (2,3,24-26), and in this group of patients prophylactic methods such as low-dose heparin, that are effective in general surgical patients, often have failed (3,27). In this study the incidence of DVT in hip fracture patients was 31% after prophylaxis with dextran 70 alone, a result which is comparable to that obtained in other similar studies (3,6). The addition of DHE to dextran 70 prophylaxis resulted in a markedly lower incidence of DVT, namely 3%. The two groups are well matched.

A high incidence of preoperative DVT has been reported in hip fracture patients (28); thus, a short interval between admission and operation, as well as early prophylaxis, seems essential in these patients. In this study prophylaxis was started preoperatively after diagnosis was made. Operation was usually performed one or two days later. The patients with hip fractures weighed considerably less than those undergoing THR (Table II) and they also received dextran on admission. Consequently, the average dextran dose in relation to weight was higher in hip fracture patients than in THR patients. It is possible that the additional increase in dextran concentration obtained by giving DHE (21) improved the efficacy of dextran prophylaxis. In most studies on DHE it has been used in combination with heparin for one week. In this study it was given during a shorter period because

we considered it of practical importance to give DHE and dextran parallel. Hip fracture patients in the combination group received DHE for a longer period than the other categories, which also may have been of importance for the difference observed.

There was no difference in the incidences of DVT after THR in the two prophylaxis groups (24 and 38% respectively). These incidences are somewhat lower than reported in other studies of this operation (3,5,29). Besides the use of dextran prophylaxis one reason might be differences in operative technique and postoperative routines. In this study a posterolateral approach to the hip was used, a method that recently has been shown to have a lower risk of DVT than the anterolateral approach (30). Further, the patients were routinely mobilized on the first day after operation. No splints or casts were used postoperatively. Because of the standardized operative technique the prerequisites for comparing blood loss during operation are best in this category of patients. Both bleeding during operation and transfusion requirements were virtually identical after the two types of prophylaxis.

The incidences of DVT were lower than anticipated after elective general surgery (4% and 13 % respectively) using either of the two types of prophylaxis, despite the fact that only major surgery was included. The incidence of DVT detected after this type of surgery with the fibrinogen test varies from 13 % to 59 % among control patients (31,4) and from 0.4 % to 31 % among patients given dextran prophylaxis in prospective controlled studies (32,33). Our results indicate that the addition of DHE to dextran prophylaxis in this type of surgery does not improve the results achieved with dextran 70 alone.

There is little information available on the natural incidence of thromboembolism after emergency general surgery (34). Although the groups are small our results indicate that the incidence of DVT after emergency surgery is of the same magnitude as after major elective surgery. No difference in efficacy can be detected between the two prophylactic methods.

Side effects of thromboembolic prophylaxis has been shown to be the most important factor influencing the surgeons' choice of prophylactic method (35). In this study dextran-induced anaphylactic reactions were prevented by using preinjection of 20 ml dextran 1 before the first infusion of dextran 70 (11,12). We observed no allergic reactions, haemostatic problems or signs of impaired renal function attributable to dextran. Significant cardiac overload possibly related to dextran occurred only in one patient, despite the high age of the patients studied. DHE injections had to be interrupted in four patients because of nausea and vomiting. DHE has been reported to induce arterial spasm (ergotism) on rare occasions (36,37), but no such side effects were observed in this study. No cardiac complications attributable to DHE were seen, and in animal experiments using radioactive microspheres the flow to the myocardium was unchanged by DHE (38).

We conclude that the addition of DHE increased the efficacy of dextran 70 prophylaxis in patients with hip fractures - a group of patients well known for having a high incidence of thromboembolic complications. However, no such potentiating effect was found after THR, elective or emergency general surgery. The addition of DHE did not change the low incidence of side effects observed after dextran prophylaxis.

ACKNOWLEDGEMENTS

We thank the orthopaedic surgeons at Kärnsjukhuset, Skövde and Danderyds Sjukhus, Danderyd for allowing us to study their patients, and Ass. Professor Göran Nylander for re-examining the phlebographies. This study was supported by the Swedish Medical Research Council (Grant no. 00759), Svenska Nationalföreningen mot hjärt- och kärlsjukdomar, Skaraborgs Läns Landstings utvecklingsfond, Stockholms Läns Landsting and Pharmacia AB, Uppsala. The skilful technical assistance of Sven Carlsson, Inger Olsson and Ingrid Söderwall is greatly appreciated.

REFERENCES

1. Koekenberg LJJL. Experimental use of macrodex as a prophylaxis against post-operative thrombo-embolism. *Bull Soc Int Chir* 1962;21:501-12.
2. Johnson SR, Bygdeman S, Eliasson R. Effect of dextran on postoperative thrombosis. *Acta Chir Scand* 1968;134(suppl 387):80-2.
3. Bergqvist D, Efsing T, Hallböök T, Hedlund T. Thrombo-embolism after elective and post-traumatic hip surgery - a controlled prophylactic trial with dextran 70 and low-dose heparin. *Acta Chir Scand* 1979;145:213-8.
4. Fey KH, Herzfeld U, Saggau W, Oehlschläger M. Post-operative Thromboseprophylaxe durch Tonisierung des kaudalen Venensystems. *Med Klin* 1975;70:1553-8.
5. Sagar S, Nairn D, Stamatakis JD, Maffei FH, Higgins AF, Thomas DP, Kakkar VV. Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total-hip replacement. *Lancet* 1976;I:1151-4.
6. Bergqvist D, Efsing T, Hallböök T, Lindblad B. Prevention of postoperative thromboembolic complications. A prospective comparison between dextran 70, dihydroergotamin-heparin and a sulphated polysaccharide. *Acta Chir Scand* 1980;146:559-68.
7. Lahnborg G. Effect of low-dose heparin and dihydroergotamine on frequency of postoperative deep-vein thrombosis in patients undergoing posttraumatic hip-surgery. *Acta Chir Scand* 1980;146:319-22.
8. Mellander S, Nordenfelt I. Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. *Clin Sci* 1970;39:183-201.
9. Rieckert H. Primäre Therapieziele bei der hypotonen Fehlgulation. *Fortschr Med* 1971;89:173-6.
10. Åberg M, Hedner U, Bergentz S-E. The antithrombotic effect of dextran. *Scand J Haematol* 1979;22(suppl 34):61-8.
11. Ljungström K-G, Renck H, Hedin H, Richter W, Rosberg B. Prevention of dextran-induced anaphylactic reactions by hapten inhibition. I. A scandinavian multicenter study on the effects of 10 ml dextran 1, 15%, administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983;149:341-8.

12. Renck H, Ljungström K-G, Hedin H, Richter W. Prevention of dextran-induced anaphylactic reactions by hapten inhibitions. III. A scandinavian multicenter study on the effects of 20 ml dextran 1, 15%, administered before dextran 70 or dextran 40. *Acta Chir Scand* 1983;149: 355-60.
13. Kakkar VV, Howe CT, Flanc C, Clarke MB. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969;II:230-3.
14. Bergqvist E, Bergqvist D, Bronge A, Dahlgren S, Hallböök T. Diagnosis of venous thrombosis in the lower limbs. A comparative study between ¹²⁵I-fibrinogen test, strain gauge pletysmography and phlebography. *Ups J Med Sci* 1973;78:191-9.
15. Bergenwald L, Eklund B, Kaijser L, Klingenström P, Westermarck L. Haemodynamic effects of dihydroergotamine during spinal anaesthesia in man. *Acta Anaesthesiol Scand* 1972;16:235-9.
16. Castenfors J, Lindblad L-E, Mortasawi A. Effect of dihydroergotamine on periferal circulation during epidural anaesthesia in man. *Acta Anaesthesiol Scand* 1975;19:79-84.
17. Kakkar VV, Stamatakis JD, Bentley PG, Lawrence D, de Haas HA, Ward VP. Prophylaxis for postoperative deep-vein thrombosis. *Jama* 1979;241:39-42.
18. Popov-Cenic S, Schander K, Etzel F. Changes in the plasma level of heparin and coagulation factors during the postoperative prophylaxis with heparin and heparin-dihydroergotamine. *Thromb Haemost* 1979;42:490.
19. Beerman B, Lahnborg G. Pharmacokinetics of heparin in healthy and obese subjects and in combination with dihydroergotamine. *Thromb Haemost* 1981;45:24-6.
20. Briel RC. Plasma heparin levels during and after hysterectomy with low-dose heparin or heparin-dihydroergotamine prophylaxis. *Thromb Res* 1980;19:513-23.
21. Lindblad B, Abisch E, Bergqvist D. The pharmacokinetics of subcutaneous dihydroergotamine with and without dextran 70 infusion. *Eur J Clin Pharmacol* 1983;24:813-8.
22. Barthel W, Markwardt F. Aggregation of blood platelets by biogenic amines and its inhibition by antiadrenergic and antiserotonergic agents. *Biochem Pharmacol* 1974;23:37-45.
23. Lindblad B, Bergqvist D, Hedner U. The effect of dihydroergotamine on the haemostatic system. *Thromb Haemost* 1983;50:67.

24. Sevitt S, Gallagher NG. Prevention of venous thrombosis and pulmonary embolism in injured patients. *Lancet* 1959;II:981-9.
25. Smyrnis SA, Kolios AS, Agnatis JK. Deep-vein thrombosis in patients with fracture of the upper part of the femur. A phlebographic study. *Br J Surg* 1973;60:447-50.
26. Morris GK, Mitchell JRA. Warfarin sodium in prevention of deep venous thrombosis and pulmonary embolism in patients with fractured neck of the femur. *Lancet* 1976;II:869-72.
27. Morris GK, Mitchell JRA. Preventing venous thromboembolism in elderly patients with hip fractures: studies of low-dose heparin, dipyridamole, aspirin, and flurbi-profen. *Br Med J* 1977;1:535-7.
28. Fenech A, Winter JH, Bennett B, Smith FW, Douglas AS. Preoperative frequency of deep venous thrombosis in patients with fractured neck of the femur. *Lancet* 1981;I:1212.
29. Barber HM, Galasko CSB, Sutton RA, Feil EJ, Edwards DH, Haynes DW. A comparative study of dextran 70, warfarin and low-dose heparin for the prophylaxis of thrombo-embolism following total hip replacement. *Postgrad Med J* 1977;53:130-3.
30. Gallus A, Raman K, Darby T. Venous thrombosis after elective hip replacement - the influence of preventive intermittent calf compression and of surgical technique. *Br J Surg* 1983;70:17-9.
31. Korvald E, Abildgaard U, Fagerhol MK. Major operations, hemostatic parameters and venous thrombosis. *Thromb Res* 1974;4:147-54.
32. Carter AE, Eban R. The prevention of postoperative deep venous thrombosis with dextran 70. *Br J Surg* 1973;60:681-3.
33. Becker J, Schampi B. The incidence of postoperative venous thrombosis of the legs. *Acta Chir Scand* 1973;139:357-67.
34. Webb P, Fok J, Kakkar VV. Venous thromboembolism in patients undergoing emergency surgery. *Br J Surg* 1981;68:807.
35. Bergqvist D. Prevention of postoperative deep vein thrombosis in Sweden. Results of a survey. *World J Surg* 1980;4:489-95.

36. van den Berg E, Walterbusch G, Gotzen L, Rumpf K-D, Otten B, Fröhlich H. Ergotism leading to threatened limb amputation or to death in two patients given heparin-dihydroergotamine prophylaxis. Lancet 1982;I:995-6.
37. Echterhoff HM, Kottman UR, Okoye XR, Rohner HG. Ergotismus - eine wichtige Komplikation in der medikamentösen Thromboembolieprophylaxe. Dtsch Med Wochenschr 1981;106:1717-18.
38. Lindblad B, Bergqvist D. Tissue blood flow and blood flow distribution after administration of dextran 70, dihydroergotamine and their combinations. Acta Chir Scand 1983;149:467-472.

PREVENTION OF POSTOPERATIVE THROMBOEMBOLIC COMPLICATIONS

*A Prospective Comparison between Dextran 70, Dihydroergotamin
Heparin and a Sulphated Polysaccharid*

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(Submitted for publication February 25, 1980)

Abstract. A prospective controlled study on prophylaxis of postoperative thromboembolic complications is presented. The study evaluated the effect of a fix combination of dihydroergotamin and low-dose heparin (DHEH) and a sulphated polysaccharid (a heparin analogue, PZ68B) in elective general and urological surgery, elective hip surgery, and hip fracture surgery. In hip surgery patients these two prophylactic methods were compared with dextran 70. Separate randomization was performed in the three groups. 427 patients were admitted; 70 were excluded according to criteria set up for the trial. Deep vein thrombosis (DVT) was diagnosed with ¹²⁵I-fibrinogen uptake test. In all patients, fatal pulmonary embolism was looked for during the first thirty postoperative days. Patients undergoing elective hip surgery were screened for pulmonary embolism with perfusion scintigraphy and X-ray preoperatively and on the 7th postoperative day. The frequency of DVT in elective general and urological surgery was 0% and 4% respectively, in elective hip surgery 9% and 10% respectively with DHEH and PZ68B. DVT in elective hip surgery was thus significant reduced with these two prophylactic methods as compared with dextran 70 prophylaxis, where the DVT-frequency was 39%. In patients operated on for hip fracture, the efficacy in reducing DVT with DHEH, PZ68B, and dextran 70 was equal, and ranged 20 to 21%. The frequency of pulmonary embolism in patients undergoing elective hip surgery was equal (11 to 18%) in spite of the differences in DVT-frequencies. Increased number of bleeding complications and increased transfusion requirement in elective surgery were noted for PZ68B given in a dose of 100 mg twice daily.

Earlier investigations showed a more effective reduction of deep vein thrombosis (DVT) in elective general and gynecological surgery with low-dose heparin (LDH) than with dextran 70 (McCarthy et al., 1974; Ruckley, 1974; Bergqvist & Hallböök, 1980; for review see Gruber et al., 1976) but fatal pulmonary embolism seems to be equally reduced (Gruber et al., 1980).

In elective hip surgery and hip fracture surgery there are different opinions of the efficacy of LDH and dextran 70 for prophylaxis of postoperative thromboembolism (Myrvold et al., 1973; Barber et al., 1977; for review see Kakkar, 1978; Bergentz, 1978). In our hands dextran 70 has been more effective in reducing major thrombosis in hip surgery (Bergqvist et al., 1979).

New methods to prevent postoperative thromboembolism are combinations of prophylactic methods or the use of heparin analogues. Promising results have been presented with the combination dihydroergotamin + LDH (DHEH, Sagar et al.,

Table I. *Reasons for exclusions*

15 (15%) patients with dextran 70, 24 (15%) patients with DHEH and 31 (19%) patients with PZ68B were excluded

	No. of patients
<i>Elective general and urological surgery</i>	
Lack of complete ¹²⁵ I-fibrinogen test	6
Prophylaxis protocol not correctly followed	9
Total	15
<i>Elective hip surgery</i>	
Lack of complete ¹²⁵ I-fibrinogen test	9
Prophylaxis protocol not correctly followed	9
Total	19
<i>Hip fracture surgery</i>	
Lack of complete ¹²⁵ I-fibrinogen test	8
Prophylaxis protocol not correctly followed	7
Hip fracture operated ad modum Ender	22
Total	70

Table II. Age, sex, operation time and side of operation, epidural analgesia

Prophylax	No. of patients	Age (y. $\pm$ S.D.)	Sex (female %)	Operation time (min $\pm$ S.D.)	Side of operation (no. right/ no. left)	Epidural analgesia (%)
<i>Elective general and urologic surgery</i>						
DHEH	54	66.8 $\pm$ 9.3	20.4	90 $\pm$ 48		30
PZ68B	52	68.1 $\pm$ 7.6	21.1	90 $\pm$ 57		30
<i>Elective hip surgery</i>						
DHEH	59	66.7 $\pm$ 8.3	66.1	85 $\pm$ 22	30/29	42
Dextran 70	56	67.5 $\pm$ 7.7	53.6	83 $\pm$ 19	27/29	54
PZ68B	53	68.7 $\pm$ 7.9	45.3	88 $\pm$ 22	31/22	60
<i>Hip fracture surgery</i>						
DHEH	25	78.5 $\pm$ 8.8	84.0	43 $\pm$ 27	14/11	
Dextran 70	29	82.4 $\pm$ 7.6	72.4	38 $\pm$ 28	14/15	
PZ68B	29	76.1 $\pm$ 7.1	82.8	32 $\pm$ 23	10/19	

1976; Kunz et al., 1977; Kakkar et al., 1979) and heparin analogues (Thomas et al., 1977; Kakkar et al., 1978; Bergqvist et al., in press).

This study evaluated the fix combination of dihydroergotamin and LDH (DHEH) and a sulphated polysaccharid (PZ68B) as prophylaxis for thromboembolism in three categories of patients: elective general and urological surgery, elective hip surgery, and hip fracture surgery. In the two groups of patients undergoing hip surgery a comparison was made with dextran 70. The frequency of pulmonary embolism in patients undergoing elective hip surgery was also evaluated.

MATERIAL

427 patients over the age of 50 years were admitted to this prospective, controlled trial. The study started in January 1978 and the last patient was included in May 1979. Separate randomization (sealed envelopes) was used within the three groups: elective general and urological surgery, elective hip surgery, and hip fracture surgery. Patients undergoing elective surgery were fully mobilized before operation. Hospitalization time before operation was at most three days. Before the trial began, strict criteria for exclusions were set up: lack of or incomplete 125 I-fibrinogen uptake test, prophylaxis protocol not correctly followed, and patients with hip fracture operated on ad modum Ender, where the 125 I-fibrinogen uptake test is inconclusive in the operated leg. Table I lists 70 excluded patients.

Table II lists age, sex, operation time, epidural analgesia, and operation side. Time between trauma and operation for patients with hip fracture did not differ according to type of prophylaxis (2.1–3.0 days). Type of operation and number of malignancies operated on in elective general and urological surgery are listed in Table III.

The study was approved by an ethical committee. Consent to participate was obtained from all patients before entrance to the trial.

PROPHYLACTIC METHODS

1. Dextran 70 (Macrodex 6% in NaCl, Pharmacia AB, Uppsala, Sweden) was given 500 ml preoperatively, 500 ml postoperatively within 12 hours after operation, and a further 500 ml on postoperative days one and three. The infusions were given intravenously in two to four hours, apart from the first which was given during operation.

2. The fix combination of dihydroergotamin (Orstanorm Sandoz AB, Täby, Sweden) and heparin (DHEH), 0.5 mg dihydroergotamin methansilphonat and 5 000 IU sodium heparin (mucosa, related to WHO stand-

Table III. Type of operation and number of malignancies in elective general and urological surgery

	DHEH	PZ68B
Surgery of colon	7	6
Ulcus ventriculi or duodeni	4	3
Cholecystectomy or choledochotomy	6 ^a	9
Explorative laparotomy	4	
Transvesical prostatectomy	11 ^a	11
Transurethral prostatectomy	11	13
Pyelolithotomy	4	3
Urolithotomy	3	3
Nephrectomy	3	3
Others	1	1
Total	54	52
Number of malignancies	16	8

^a Patient with DVT.

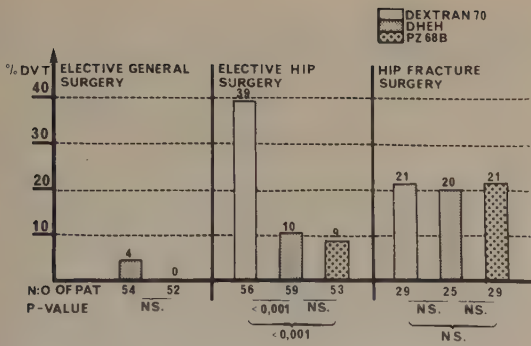


Fig. 1. Frequency of DVT in 357 patients.

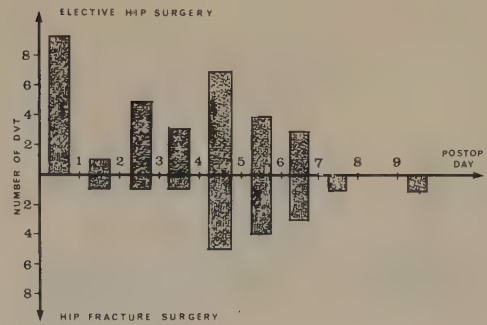


Fig. 2. Onset of DVT in hip surgery.

and III) was dissolved in saline solution. The prophylaxis began two hours before surgery; the second injection was given the same day not earlier than six hours after operation; thereafter every 12 hours during the first eight postoperative days. The injections were administered subcutaneously in the lateral aspect of the thigh.

3. The sulphated polysaccharid (PZ68B), sodium pentosan polysulphate, (Pharmacia AB, Uppsala, Sweden) was administered subcutaneously in the same way as DHEH and was dissolved in saline solution and given in a dose of 100 mg two hours before operation and then as for DHEH.

All subcutaneous injections were given with a 0.6 × 25 mm needle. A checklist for control of given prophylaxis was made for each patient. The exact time of administration was registered.

In patients with hip fracture, the prophylaxis began as soon as possible after arrival at hospital (within 3 hours). Dextran 70 was given 500 ml every second day until operation, and DHEH and PZ68B as subcutaneous injection every 12 hours. From operation on the prophylaxis was given as in elective surgery.

There were no differences in physiotherapy or time of mobilization (usually the first postoperative day) between the prophylactic groups.

DIAGNOSTIC METHODS

Diagnosis of deep vein thrombosis. DVT was detected with the ^{125}I -fibrinogen test. External scanning with a scintillation counter was performed mainly according to Kakkar et al. (1969) with slight modifications (Bergqvist et al., 1973). Both legs were scanned at eight different points at least every second day during the first eight postopera-

tive days. In elective surgery, scanning preoperatively was also performed.

Each patient undergoing elective surgery received 100 μCi of Amersham's fibrinogen intravenously on the day before operation. Patients with hip fracture were injected as soon as the scanning could begin and before surgery. If necessary, the ^{125}I -fibrinogen dose was repeated. Measured activity of the external scanning was correlated to the precordial activity. The thyroid was blocked with oral KI 150 mg or intravenous NaI 3 ml given daily beginning preoperatively and thereafter during the first 14 postoperative days.

The criterion for diagnosis of DVT was a difference in count at any site of 20% or more from that at an adjacent count point on the same leg or the same position on the opposite limb. This difference should persist or increase in the subsequent 24 hours.

Criteria for major thrombosis were bilateral calf thrombi, thigh thrombi, and/or pulmonary embolism (Bergqvist & Dahlgren, 1973).

Diagnosis of pulmonary embolism. Fatal pulmonary embolism was looked for during the first 30 postoperative days in all patients. In patients undergoing elective hip surgery, X-ray of the lung and lung-perfusion scintigraphy were performed preoperatively and on the seventh postoperative day. After an injection of 2–4 μCi ^{99}Tc -labelled macroaggregated human albumin, scanning of the lung in four projections was made: anterior, posterior and left and right lateral positions.

Criterion for scintigraphic diagnosis of pulmonary embolism was a perfusion defect of at least segment size not noted preoperatively and where X-ray did not show signs of inflammatory pulmonary disease. A scintigraphic ir-

Table IV. Major thrombi (bilateral calf, thigh thrombi and/or pulmonary emboli) in hip surgery patients

	Number of major thrombi (% of patients)		
	DHEH	Dextran 70	PZ68B
Elective hip surgery	6 (10%)	15 (27%)	6 (11%)
Hip fracture surgery	2 (8%)	3 (10%)	6 (21%)

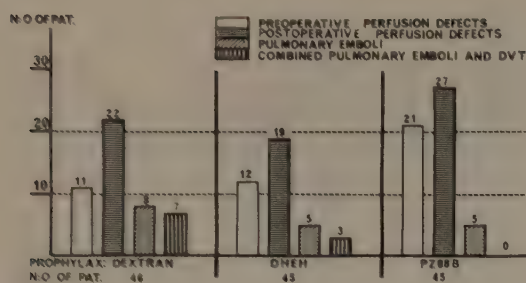


Fig. 3. Frequency of scintigraphically diagnosed pulmonary embolism in elective hip surgery.

regular uptake was not considered diagnostic of embolism.

Complications. Peroperative bleeding was measured from the amount of blood in suction drainage and the content of blood in the swabs.

Transfusion requirement was calculated from the needs during and after surgery. One unit of blood contains 400 ml whole blood. Haematoma formation at injection site was recorded with the scintillation equipment in patients receiving their prophylaxis subcutaneously (Bergqvist & Hallböök, 1978).

All patients with bleeding complications needing surgical intervention (reoperation, debridement) were noted. Other side effects, such as infectious complications and

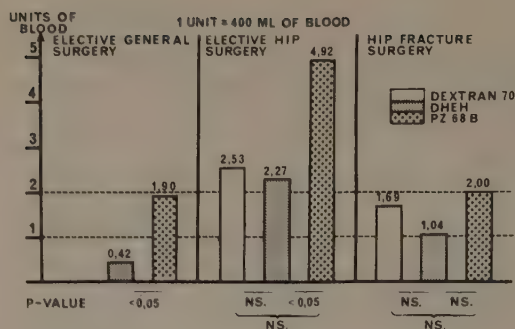


Fig. 4. Transfusion requirement.

spontaneous reaction of pain from subcutaneous injections or bruising at injection site, were listed. Hospitalization time was recorded. Diagnostic evaluations were made without knowledge of the prophylactic group randomization.

Statistical methods. Fischer's exact test and χ^2 -test were used for significance evaluation.

RESULTS

Fig. 1 lists the frequency of DVT in each prophylactic group and according to type of surgery. In elective general and urological surgery, two out of 54

Table V. Cause of death

	Age	Sex	Postop. day	Prophylaxis
<i>Elective general and urological surgery</i>				
1. Operated colon malignancy with leakage at the anastomosis and peritonitis	78	M	18	PZ68B
2. Operated transvesical prostatectomy with signs of myocardial infarction. No post-mortem examination	81	M	9	DHEH
3. Operated colon malignancy with colonic and ventricular resection. Cardiac failure. No post-mortem examination	75	M	12	DHEH
<i>Elective hip surgery</i>				
4. Myocardial infarction	71	F	9	PZ68B
5. Pneumonia. DVT and pulmonary embolism	76	M	25	PZ68B
<i>Hip fracture surgery</i>				
6. Myocardial infarction. No post-mortem exam.	92	F	10	DHEH
7. Pneumonia and cardiac failure	94	F	10	Dextran 70
8. Myocardial infarction and embolus in a. femoralis	96	F	24	DHEH
9. Left femoral DVT and pulmonary embolism. Steroid treated giant cell arteritis and hypothyreosis	82	F	14	DHEH
10. Cerebral infarction with cerebral oedema. Pulmonary emboli in one branch of a. pulmonary dx.	83	F	18	PZ68B
11. Cardiac failure	70	F	8	PZ68B
12. Cardiac failure. DVT with iliac vein engagement and pulmonary embolism	82	F	15	PZ68B
13. Cerebral infarction. No post-mortem exam.	81	M	19	PZ68B

Table VI. *Peroperative bleeding according to type of surgery and given prophylaxis (ml). (Mean $\pm$ S.D.)*

	Dextran 70	DHEH	PZ68B
Elective general and urological surgery	—	372 $\pm$ 441	403 $\pm$ 394
Elective hip surgery	728 $\pm$ 370	793 $\pm$ 415	757 $\pm$ 375
Hip fracture surgery	134 $\pm$ 202	195 $\pm$ 424	129 $\pm$ 201

patients on DHEH and none out of 52 patients on PZ68B developed DVT. In elective hip surgery, both DHEH and PZ68B significantly reduced the frequency of DVT compared with dextran 70 ($p < 0.001$). In hip fracture surgery, the frequency was the same with the three methods (20–21%). To these figures should be added two patients who after completion of ^{125}I -fibrinogen test developed clinical signs of DVT. One patient on PZ68B-prophylaxis undergoing elective urological surgery developed clinical signs of DVT and pulmonary embolism 14 days after operation. Thermography showed a calf thrombus and lung perfusion scintigraphy showed defects over segment size. One patient on dextran 70-prophylaxis developed clinical signs of DVT 15 days after elective hip surgery. Anticoagulant therapy was begun without confirmation of the clinical diagnosis.

Table IV shows the frequency of major thrombosis. In elective hip surgery, both DHEH and PZ68B significantly reduced the frequency of major thromboembolic complications compared with dextran 70 ($p < 0.05$).

Onset of DVT

Onset of DVT varied according to whether elective or emergency surgery was performed. A tendency

of delayed onset of DVT was seen in hip fracture surgery compared with elective hip surgery. Fig. 2 illustrates.

Fatal pulmonary embolism

13 patients in the study died (Table V). Nine were examined at postmortem (autopsy rate 70%). Fatal pulmonary embolism was seen in three, one with DHEH (no. 9) and two with PZ68B-prophylaxis (nos. 5, 12). Postmortem on another patient with PZ68B-prophylaxis showed associated pulmonary embolism (no. 10). One of the fatal emboli was seen after elective hip surgery; the others after hip fracture surgery.

Scintigraphically diagnosed pulmonary embolism

In 136 of 164 patients undergoing elective hip surgery, complete screening for pulmonary embolism was made (Fig. 3). Preoperatively an irregular uptake was seen in 35 patients (25%). In another nine patients (7%), the defects were of at least segmental size, all being unchanged in the postoperative investigation. The frequency of scintigraphically diagnosed pulmonary embolism ranged

Table VII. *Haematoma at injection site. The figures correlated to cardiac activity in %. (Mean $\pm$ S.D.)*

	Postoperative day					
	1	2	3	4	5	6
<i>Elective general and urological surgery</i>						
DHEH	26 $\pm$ 10	27 $\pm$ 12	33 $\pm$ 12	33 $\pm$ 12	38 $\pm$ 26	45 $\pm$ 35
PZ68B	32 $\pm$ 10	35 $\pm$ 12	36 $\pm$ 15	40 $\pm$ 25	40 $\pm$ 21	48 $\pm$ 31
<i>Elective hip surgery</i>						
DHEH	36 $\pm$ 19	42 $\pm$ 22	46 $\pm$ 23	51 $\pm$ 28	52 $\pm$ 30	56 $\pm$ 27
PZ68B	46 $\pm$ 21	74 $\pm$ 156	51 $\pm$ 25	60 $\pm$ 29	66 $\pm$ 39	65 $\pm$ 42
<i>Hip fracture surgery</i>						
DHEH	17 $\pm$ 8	26 $\pm$ 8	25 $\pm$ 11	29 $\pm$ 10	36 $\pm$ 12	38 $\pm$ 17
PZ68B	17 $\pm$ 6	26 $\pm$ 12	31 $\pm$ 15	34 $\pm$ 14	34 $\pm$ 15	51 $\pm$ 31

Table VIII. Bleeding complications

	Transfusion requirement units	Prophy- laxis
<i>Elective general and urological surgery</i>		
Transvesical prostatectomy, reoperated	13	PZ68B
Haemicolectomy, reoperated and artery ligated	11	PZ68B
Cholecystectomy, reoperated with evacuation of haematoma	7	PZ68B
Ureterolithotomy with debridement of wound haematoma	2	PZ68B
<i>Excluded patients:</i>		
Transvesical prostatectomy, reoperated 3 times	30	PZ68B
Pyolithotomy, reoperated and artery ligated	14	PZ68B
Transvesical prostatectomy, reoperated	18	PZ68B
Cholecystectomy, reoperated and artery ligated	10	PZ68B
Explorative laparotomy for malignancy, reoperated	2	DHEH
<i>Elective hip surgery</i>		
Wound bleeding where thrombocyasthenia develops and general bleeding was seen. Reoperation	28	PZ68B
Pulmonary embolism where therapy with heparin was given and general bleeding was seen, haematoma in the wound was evacuated	11	PZ68B
Wound bleeding, suture	6	PZ68B
Wound bleeding, suture	8	PZ68B
Wound haematoma, evacuated	6	PZ68B
Wound bleeding, suture	6	DHEH
<i>Excluded patient:</i>		
Wound bleeding, reoperated. Develops thrombocyasthenia	20	PZ68B
<i>Hip fracture surgery</i>		
Wound haematoma, evacuated	7	PZ68B
Wound haematoma, evacuated	4	PZ68B
<i>Excluded patient:</i>		
Wound haematoma, debridement	5	PZ68B

between 11 and 18%. There was no significant difference between the groups. The combination of ¹²⁵I-fibrinogen positive DVT and a scintigraphically diagnosed pulmonary embolism was seen in 10 out of 18 patients.

Complications

No significant differences were seen in perioperative bleeding (Table VI).

Increased transfusion requirement was seen with PZ68B-prophylaxis compared with DHEH-prophylaxis in elective surgery (Fig. 4). In elective hip surgery, transfusion requirement was greater for PZ68B than for dextran 70, although not significant. In hip fracture surgery, the transfusion requirements were equal.

Haematoma at injection site was measured with the scintillation equipment (Table VII). No differences were seen.

Bleeding complications needing surgical intervention were seen in 19 patients. Seven of them were excluded according to the criteria set up for exclusions, but only two of them were excluded due to the fact that the prophylactic treatment was set out. 17 of the 19 received PZ68B and two DHEH.

Table IX. Other side effects

Two out of eleven patients with wound infection showed DVT

	Type of prophylaxis		
	DHEH	Dextran 70	PZ68B
Bruising at injection site	2		2
Pain of injection	1		1
Allergic reaction		1	
Wound infection	6	1	4

prophylaxis ($p < 0.001$). Table VIII lists all patients with bleeding complications.

Other side effects were few (Table IX).

DISCUSSION

New trends in improving the efficacy of thromboembolic prophylaxis that have shown promising results are the combination of LDH and dihydroergotamin (Sagar et al., 1976; Kunz et al., 1977; Kakkar et al., 1979), or the use of heparin analogues (Thomas et al., 1977; Kakkar et al., 1978; Bergqvist et al., in press).

In the combination of dihydroergotamin and LDH, the effects of dihydroergotamin are added to the antithrombotic properties of heparin. Dihydroergotamin increases the tone of capacitance vessels and also increases the velocity of blood flow within them (Mellander et al., 1970; Mühe et al., 1974).

PZ68B, a sulphated polysaccharid (sodium pentosan polysulphate), is a polymer of pentosan with a medium molecular weight of 4 100. It has shown a stable inhibition of the activation of factor X (Bergqvist & Nilsson, in press).

Our study evaluated these two new prophylactic methods in different types of surgery and compared their efficacy with dextran 70 in hip surgery in reducing postoperative thromboembolic complications. Before the trial began statistically correct design of it was made and the necessary number of patients was decided in cooperation with a biostatistician. ^{125}I -fibrinogen test is a reliable screening method for detection of postoperative deep vein thrombosis in general surgery. Hip surgery on the contrary presents a diagnostic problem. There are two types of thrombi developing after hip operations: bilateral calf vein thrombi and proximal thrombi in the operated leg (Culver et al., 1970; Bergqvist et al., 1976; Nillius & Nylander, 1979). And it is the presence of *isolated and solitary* proximal thrombi which is crucial for the use of the fibrinogen test in these patients. However, their frequency is rather low, which has been shown phlebographically (Nillius & Nylander, 1979) as well as at autopsy (Morris & Mitchell, 1977). With exception of the study by Harris et al. (1975) the fibrinogen test has shown both a sensitivity and a specificity in comparison with phlebography which makes it acceptable as a screening method for diagnosis of postoperative thrombosis also in hip pa-

tients (Field et al., 1972; Myrvold et al., 1973; Bergqvist et al., 1973; Bockslaff et al., 1974; Bergqvist et al., 1976; London et al., 1978).

The frequency of deep vein thrombosis in elective general and urological surgery was very low for both DHEH and PZ68B. In elective hip surgery, both DHEH and PZ68B were significantly more effective than dextran 70 in prevention of DVT ($p < 0.001$) and major thromboembolic complications ($p < 0.05$). In a study two years earlier from the same hospital, the control group frequency was 27% in elective general surgery and 63% in elective hip surgery (Bergqvist et al., 1979; Bergqvist & Hallböök, 1980). The results for DHEH corresponds to other reports (Sagar et al., 1976; Kunz et al., 1977, Kakkar et al., 1979). Both Sagar et al. (1976) and Kakkar et al. (1979) used 0.5 mg DHE + 5 000 IU heparin every 8 hours in elective hip surgery but in our present study the same dose was given every 12 hours. Despite this difference, the results seem to correspond. In view of the increased number of bleeding complications with higher heparin administration (Bergqvist, 1979; Hohl et al., 1979) it seems reasonable to recommend the 12-hourly administration until a controlled trial has shown the benefit of the 8-hourly administration.

The frequency of DVT in hip fracture patients was equal between DHEH, PZ68B, and dextran 70. Major thrombi were also equally distributed. Earlier studies showed more effective reduction of major thrombi with dextran 70-prophylaxis (Bergqvist & Dahlgren, 1973; Bergqvist et al., 1979) and studies using phlebography also showed the most favourable reduction of DVT with dextran 70 (Ahlberg et al., 1968; Johnson et al., 1968). Therefore dextran 70 is recommended for prophylaxis of thromboembolic complications after hip fracture surgery. DHEH, however, seems to be of equal effect.

In our investigation, the frequency of DVT was higher in elective hip surgery than in hip fracture surgery for patients with dextran 70 prophylaxis. This was also noted by Bergqvist et al. (1979). No certain explanation can be given, but there are differences between the groups in age and extent of trauma.

There is a tendency that the onset of DVT is earlier in elective hip surgery than in hip fracture surgery especially when receiving DHEH or PZ68B-prophylaxis. Twelve out of twenty-two

(55%) patients on dextran 70-prophylaxis undergoing elective hip surgery who developed DVT had an onset of DVT after the fourth postoperative day. The effect of further dextran 70-infusions, at least on the fifth postoperative day (Everts & Feil, 1971), can only be speculated on.

Prophylaxis in patients with hip fracture was begun as soon as possible after arrival at hospital. According to the low number of DVT during the first three postoperative days and the fact that others also have shown the benefit of early start of prophylaxis, it seems reasonable to recommend that prophylaxis should be started as soon as possible after the fracture trauma (Bergqvist et al., 1973; Myhre et al., 1973; Bergqvist & Dahlgren, 1973).

The frequency of scintigraphically verified pulmonary embolism ranged 11 to 18% and did not differ between the prophylactic groups. This corresponds to what Browse et al. found with a combination of ventilation and perfusion scintigraphy and is lower than that found by Lahnberg et al. (1974) and Nillius (1978) using only perfusion scintigraphy. Our study only considered scintigraphic defects over segment size as pulmonary embolism. It is known that the sensitivity is high but the specificity is low with lung perfusion scintigraphy. Our study also included preoperative lung perfusion scintigraphy. In 7% of these there were defects of at least segmental size. A preoperative examination thus seems to increase the specificity for lung perfusion scintigraphy, but if we compare patients on dextran 70 prophylaxis from an earlier study in the same hospital where preoperative perfusion scintigraphy was not made, the frequency of scintigraphically diagnosed pulmonary embolism is still comparable (21% versus 18%) (Bergqvist et al., 1979).

Eight patients with scintigraphically diagnosed pulmonary emboli did not have any DVT diagnosed with the ^{125}I -fibrinogen test. In many reports (Butterman et al., 1977) only patients with DVT are screened for pulmonary embolism. Our data indicate that all patients should be investigated for correct evaluation of the frequency of pulmonary embolism.

No patients less than 70 years of age died during the follow-up period. The mortality was 2.8% in elective general and urological surgery, 1.2% in elective hip surgery and 9.6% in hip fracture surgery. There was significant less mortality in hip surgery patients on dextran 70-prophylaxis than on PZ68B-prophylaxis ($p < 0.05$). The frequency of

fatal pulmonary emboli was 0.84% in the total material.

The number of bleeding complications and the increased transfusion requirement for PZ68B is unacceptable and PZ68B-prophylaxis in a dose of 100 mg twice daily cannot be recommended in patients undergoing elective surgery. However, hip fracture patients show no differences in the bleeding parameters between the groups. This could be due to the already activated coagulation system before the first dose of PZ68B. In another study on hip fracture patients, and in elective general surgery a reduced dose of PZ68B seems to have the same thromboembolic prophylactic effect without bleeding complications (Bergqvist et al., in press). Transfusions were generally made to keep haematocrit as close to 30 as possible which means that the haemodiluted dextran patients could be over-transfused.

To summarize: we conclude that the combination of dihydroergotamin and low-dose heparin is efficient in reducing thromboembolic complications in elective surgery. Patients undergoing surgery for hip fracture should be recommended to have dextran 70-prophylaxis, beginning as soon as possible after the fracture trauma. The heparin analogue PZ68B effectively reduced thromboembolic complications, but in a dose of 100 mg twice daily, there was an unacceptably large number of bleeding complications; a reduction of this dose is recommended when using PZ68B for prophylaxis of postoperative thromboembolic complications, at least in elective surgery.

ACKNOWLEDGEMENT

The skilful technical assistance of Mrs Ingrid Söderwall is greatly appreciated.

REFERENCES

- Ahlberg, Å., Nylander, G., Robertson, B., Cronberg, S. & Nilsson, I. M. 1968. Dextran in prophylaxis of thrombosis in fractures of the hip. *Acta Chir Scand*, Suppl. 387, 83.
- Barber, H. M. L., Galasko, C. S. B., Sutton, R. A., Feil, E. J., Edwards, P. H., Haynes, D. W. & Bentley, G. 1977. A comparative study of dextran-70, warfarin and low-dose heparin for the prophylaxis of thromboembolism following total hip replacement. *Postgrad Med J* 53, 130.
- Bergentz, S. E. 1978. Dextran in the prophylaxis of pulmonary embolism. *World J Surg* 2, 19.

- Bergqvist, E., Bergqvist, D., Bronge, A., Dahlgren, S. & Hallböök, T. 1973. Diagnosis of venous thrombosis in the lower limbs. A comparative study between ^{125}I -fibrinogen test, strain gauge plethysmography and phlebography. *Uppsala J Med Sci* 78, 191.
- Bergqvist, D. 1979. Prophylaxis of postoperative thromboembolic complications with low-dose heparin. An analysis of different administration intervals. *Acta Chir Scand* 145, 7.
- Bergqvist, D., Bergentz, S. E., Kristiansen, P. & Nilsson, I. M. 1979. En ny trombosprofylaktisk möjlighet. Effekten av en sulfaterad polysaccarid. *Sv Kirurgi*. In press.
- Bergqvist, D. & Dahlgren, S. 1973. Leg vein thrombosis diagnosed by ^{125}I -fibrinogen test in patients with fracture of the hip: a study of the effect of early prophylaxis with dicumarol or dextran-70. *VASA* 2, 121.
- Bergqvist, D., Efsing, H. O., Hallböök, T. & Hedlund, T. 1979. Thromboembolism after elective and post-traumatic hip surgery—a controlled prophylactic trial with dextran 70 and low-dose heparin. *Acta Chir Scand* 145, 213.
- Bergqvist, D. & Hallböök, T. 1978. A comparison between subcutaneous low-dose sodium and calcium heparin. Prophylaxis of postoperative deep vein thrombosis and side effects of treatment. *Acta Chir Scand* 144, 339.
- Bergqvist, D. & Hallböök, T. 1980. Prophylaxis of postoperative thrombosis in a controlled trial comparing dextran 70 and low-dose heparin. A study with the ^{125}I -fibrinogen test. *World J Surg* 4, 239.
- Bergqvist, D. & Nilsson, I. M. 1980. A sulphated polysaccharide. The effect in vivo and in vitro on the haemostatic system in healthy volunteers. In press.
- Bergqvist, D., Elvelin, R., Eriksson, U. & Hjelmstedt, A. 1976. Thrombosis following hip arthroplasty. A study using phlebography and ^{125}I -fibrinogen test. *Acta Orthopaed Scand* 47, 549.
- Bockslaff, H., Barhels, M., Stolle, E., Trentz, O., Wupermann, Th. & Zech, G. 1974. Frühdiagnose von Beinvenenthrombosen mit dem Radiofibrinogen-Test bei Patienten mit alloplastischen Hüftgelenkersatz. *Munch Med Wschr* 116, 1397.
- Browse, N. L., Clemenson, G., Bateman, N. T., Gaunt, J. I. & Croft, D. N. 1976. Effect of intravenous dextran-70 and pneumatic leg compression on incidence of postoperative pulmonary embolism. *Brit Med J* 2, 1281.
- Butterman, G., Theisinger, W., Weidenbach, A., Hartung, U., Wenzel, E. & Pabst, H. W. 1977. Quantitative Bewertung der postoperativen Thromboembolieprophylaxe. *Med Klin* 72, 1624.
- Everts, C. & Feil, E. 1971. Prevention of thromboembolic disease after elective surgery of the hip. *J Bone Joint Surg* 53A, 1271.
- Field, E. S., Nicolaides, A. N., Kakkav, V. V. & Crellin, R. Q. 1972. Deep-vein thrombosis in patients with fractures of the femoral neck. *Br J Surg* 59, 377.
- Gruber, U. F., Sturm, V., Rem, J., Schaub, N. & Rittman, W. W. 1975. The present state of prevention of postoperative thromboembolic complications. *Bibl Haemat* 41, 98.
- Gruber, U. F., Saldeén, T., Brokop, T., Eklöf, B., Eriksson, I., Goldie, I., Gran, L., Hohl, M., Jonsson, T., Kristensen, S., Ljungström, K. G., Lund, T., Maartman Moe, H., Svensjö, E., Thomson, D., Torhorst, J., Trippestad, A. & Ulstein, M. 1980. Comparison of the incidence of fatal postoperative pulmonary embolism with dextran 70 and low-dose heparin prophylaxis. *Brit Med J* 1, 69.
- Harris, W., Salzmann, E., Athanasoulis, C., Waltman, A., Baum, S., DeSanctis, R., Potsaid, M. & Sise, H. 1975. Comparison of ^{125}I -fibrinogen count scanning with phlebography for detection of venous thrombi after elective hip surgery. *N Engl J Med* 292, 665.
- Hohl, M. K., Lüscher, K. P. & Gruber, U. F. 1979. Prophylaxis of deep vein thrombosis in gynecology. *Thrombos Haemostas* 42, 303.
- Johnson, S. R., Bygdeman, S. & Eliason, R. 1968. Effect of dextran on postoperative thrombosis. *Acta Chir Scand*, Suppl. 387, 80.
- Kakkav, V. V. 1978. The current status of low-dose heparin in the prophylaxis of thrombophlebitis and pulmonary embolism. *World J Surg* 2, 3.
- Kakkav, V. V., Howe, C. T., Flanc, C. & Clarke, M. B. 1969. Natural history of postoperative deep vein thrombosis. *Lancet* ii, 230.
- Kakkav, V. V., Lawrence, D., Bentley, P. G., de Haas, H. A., Ward, V. P. & Scully, M. F. 1978. A comparative study of low doses of heparin and a heparin analogue in the prevention of postoperative deep vein thrombosis. *Thromb Res* 13, 111.
- Kakkav, V. V., Stamatkis, J. D., Bentley, P. G., Lawrence, D., de Haas, H. A. & Ward, V. P. 1979. Prophylaxis for postoperative deep-vein thrombosis. Synergistic effect of heparin and dihydroergotamine. *JAMA* 241, 39.
- Kunz, S., Drähne, A. & Briel, R. C. 1977. Prophylaxe der postoperativen Thromboembolie-Erfahrungen mit Heparin-Dihydroergot[®] in der Gynäkologie. In *Postoperative Thromboemboli-Prophylaxe*. 6 Rothenburger Gespräch, 20–21 Mai 1977 (ed. H. W. Pabst & G. Maurer), pp. 133–144. Schattauer Verlag, Stuttgart and New York.
- Lahnborg, G., Friman, L., Bergström, K. & Lagergren, H. 1974. Effect of low-dose heparin on incidence of postoperative pulmonary embolism detected by photoscanning. *Lancet* i, 329.
- London, J. R., McGarrity, G., Vallance, R., Baylis, A. C. & Graham, J. 1978. The fibrinogen uptake test after hip surgery. *Br J Surg* 65, 616.
- McCarthy, T. G., McQueen, J., Johnstone, F. D., Weston, J. & Campbell, S. 1974. A comparison of low-dose subcutaneous heparin and intravenous dextran 70 in the prophylaxis of deep vein thrombosis after gynaecological surgery. *J Obstet Gynaecol Br Commonwealth* 81, 486.
- Mellander, A. & Nordenfelt, I. 1970. Comparative effects of dihydroergotamine and noradrenaline on resistance, exchange and capacitance functions in the peripheral circulation. *Clin Sci* 39, 183.
- Morris, G. K. & Mitchell, J. R. A. 1977. Evaluation of

- ¹²⁵I-fibrinogen test for venous thrombosis in patients with hip fractures: comparison between isotope scanning and necropsy finding. *Br Med J* 1, 264.
- Mühe, E., Burghardt, K.-H., Kolb, W. & Strobel, G. 1975. Eine neue Methode zur Prophylaxe postoperativer Venenthrombosen. *Klinikerzt* 4, 88.
- Myhre, H. O., Støren, E. & Auensen, C. 1973. Pre- or postoperative start of anticoagulation prophylaxis in patients with fractured hips? *J Oslo City Hosp* 23, 15.
- Myrvold, E. E., Person, J.-E., Svensson, B., Wallensten, S. & Vinterlöf, K. F. 1973. Prevention of thrombo-embolism with dextran 70 and heparin in patients with femoral neck fractures. *Acta Chir Scand* 139, 609.
- Nillius, A. 1978. *Thromboembolism after total hip replacement*. Thesis, Malmö.
- Ruckley, C. V. 1974. Heparin versus dextran in the prevention of deep vein thrombosis. A multi-unit controlled trial. *Lancet* ii, 188.
- Sagar, S., Stamatkis, J. D., Higgins, A. F., Nairn, D., Maffei, F. J., Thomas, D. P. & Kakkar, V. V. 1976. Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total-hip replacement. *Lancet* i, 1151.
- Thomas, D. P., Lane, D. A., Michalski, R., Johnson, E. A. & Kakkar, V. V. 1977. A heparin analogue with specific action on antithrombin III. *Lancet* i, 120.

THE THROMBOPROPHYLACTIC EFFECT OF GRADED ELASTIC COMPRESSION STOCKINGS IN COMBINATION WITH DEXTRAN 70.

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ABSTRACT

With the aim of analyzing if graded elastic compression stockings reduced the frequency of postoperative thrombosis in patients with dextran 70 prophylaxis 80 patients above 50 years of age were studied. All patients received a total amount of 2000 ml of dextran 70 during 3 days and according to a random table one of the patient's legs was applied with a graded compression stocking for one week. Thrombosis development was screened with the ^{125}I -fibrinogen test. Eight patients developed thrombosis, one in the thigh and seven in the calf, all localized to the unstockinged leg which is significantly more than the zero frequency in the stockinged leg. No untoward effects of this combination prophylaxis were noted.

INTRODUCTION

Dextran infusion is one of the established methods of reducing fatal pulmonary embolism (1-2) and in this respect it is comparable with low-dose heparin (3), or low-dose heparin in combination with dihydroergotamine (4). It is, however, less effective than low-dose heparin in reducing deep vein thrombosis, as detected with the ^{125}I -fibrinogen test after general surgery. In patients undergoing general surgery the use of graded compression stockings alone has been found effective in preventing deep vein thrombosis (5-7).

The aim of this study has been to ascertain whether the thromboprophylactic effect of dextran 70 would be enhanced when used in combination with graded elastic compression.

MATERIALS AND METHODS

Eighty-eight patients (46 male and 42 female) over 50 years of age were studied. Eight patients (4 male, 4 female) were excluded for various technical reasons. Analysis is thus based on 80 patients (42 male, 38 female). In eleven patients there were no obvious preoperative risk factor except age for thrombo-embolic

complications. Twenty-three patients had varicose veins, 44 malignant disease and 13 major cardio-pulmonary disease. Six patients had a history of previous thromboembolism. The median age was 68 years (range 52-85 years). The operations performed are listed in Table I, all patients being operated on under general anaesthesia.

All patients gave their informed consent to participate in the study which was approved by the medical ethics committee, University of Lund, Sweden.

TABLE I

Operations performed, number of malignancies and thrombosis (DVT).

	No. of patients	No. of patients with malignancy	No. of patients with DVT
Cholecystectomy	16	0	1
Choledocholithotomy	11	0	1
Colon resection	31	22	4
Abdomino-perineal rectumamputation	7	7	0
Low anterior resection	4	4	1
Bilio-intestinal shunt	4	4	1
Whipple's operation	1	1	1*
Others	6	1	0

*) Patient developing thrombosis after completed scanning of ^{125}I -fibrinogen.

Prevention of thrombosis

All patients received dextran 70 (Macrodex, Pharmacia AB, Uppsala, Sweden) in a dose of 500 ml intra-operatively, 500 ml immediately postoperatively and 500 ml on the first and third postoperative day. To prevent anaphylactic reactions to dextran (8-9), all patients were also given 20 ml dextran 1 (Promiten, Pharmacia AB, Uppsala, Sweden) intravenously before the first infusion of dextran 70.

According to a random table one of the patient's legs was applied with a graded compression stocking (Comprinet S AntiThrombose-Strumpf, Beiersdorf AB, Kungsbacka, Sweden), stockings being applied to 41 right and 39 left legs. The stockings are of full length and individually fitted, their size (nine sizes available) being determined in accordance with the manufacturer's recommendations. Properly applied, they have a pressure of 16 mm Hg at the ankle, and 7 mm Hg in the groin. The stockings

were put on the evening before operation and kept on for 7 days, with a change to a fresh stocking on postoperative day 3. Dextran and stockings were the only prophylactic methods used apart from early mobilization in accordance with the ward routine.

Diagnostic screening

The ^{125}I -fibrinogen test was used essentially as described by Kakkar et al (10) and Bergquist et al (11). The fibrinogen (100 μCi ; Amersham, England) was injected and the first measurement made pre-operatively. Screening was continued for seven days, the second measurement being made on the first postoperative day, and subsequent ones every second day - or every day where tests were positive. An increase in uptake of 20 % or more, for more than 24 hours, as compared with adjacent points or corresponding points on the opposite leg, was considered diagnostic evidence of thrombosis. The thyroid uptake of ^{125}I was blocked with oral KI 200 mg or intravenous NaI 150 mg, first given before fibrinogen injection and continued for 10 days.

All patients were kept under observation for 30 days with regard to fatal pulmonary embolism and postoperative complications. Intra-operative blood loss was estimated by the anaesthesiologist and postoperative blood transfusion requirement noted as well as other complications which could be attributable to the prophylaxis.

The χ^2 test was used in statistical calculations.

RESULTS

The ^{125}I -fibrinogen test was positive in eight patients with a median age of 65 years (range 57-77), giving a thrombosis frequency of 10 %. The types of operation for thrombosis patients are listed in Table I. There were six left-sided and two right-sided thrombi, all of which developed in unstockinged legs. This is significantly different from the zero frequency in stockinged legs ($p < 0.02$). One thrombus developed in the thigh, the others in the calf. Two patients with thrombosis had benign disease, six malignant. Patients developing thrombosis had had a longer preoperative stay in hospital than those who did not (Table II). Duration of operation, peroperative haemorrhage, and postoperative transfusion requirements did not vary between patients with thrombosis and those without. Thrombosis appeared on postoperative day 3 (median, range 1-6 days).

In one patient (male 62 years of age), operated on for carcinoma of the pancreas (Whipple), clinical signs of thrombosis developed in the unstockinged leg on the eighth postoperative day. Though a previous fibrinogen test had been negative the thrombosis was verified by phlebography.

In one cholecystectomized patient (female 63 years of age) symptoms suggesting pulmonary embolism developed on postoperative day 17. The ^{125}I -fibrinogen test had been negative. Perfusion-ventilation scintigraphy confirmed the diagnosis of pulmonary embolism. After peroral anticoagulation the patient made an uneventful recovery.

TABLE II

Some comparisons between patients developing thrombosis (DVT) and the total material. Median and range.

	Total material	Patients with DVT
Preoperative hospitalization time (days)	2.5 (1-20)	7.5 (1-28)
Duration of operation (min)	140 (50-495)	128 (80-185)
Peroperative haemorrhage (ml)	300 (0-3500)	300 (100-800)
Postoperative transfusions (units)	0 (0-10)	0 (0-1)

Two patients died postoperatively (2.5 %), one 74-year-old female on the second postoperative day because of cardiac insufficiency and one 74-year-old female on the 22nd day because of the infiltration of a gallbladder cancer into the duodenum causing haemorrhage. Neither of them had thromboembolic complications at autopsy.

In four cases (5 %), haemorrhage was considered abnormal. One wound haematoma evacuated spontaneously. In one patient undergoing abdomino-perineal rectum amputation a tamponade was needed to stop presacral bleeding. In two cases without postoperative bleeding complications the surgeon considered bleeding from the gallbladder liver bed to be excessive and in another patient there was bleeding from the wound edges.

In ten patients (12.5 %), there were different infectious complications: six wound infections and one each of cholangitis, subphrenic abscess, sepsis and urinary tract infection, the patient with cholangitis developing thrombosis.

There were no re-operations, no allergic complications were noted, nor were there any complications which could be directly related to the prophylactic program.

DISCUSSION

This study has shown that it is possible to achieve a very low frequency of postoperative deep vein thrombosis after general abdominal surgery by the combined use of graded elastic compression stockings and dextran 70. Because of the multiplicity of factors involved in the thrombotic disease it is sensible to test and evaluate different prophylaxis combinations. Clearly, the use of compression stockings and dextran is a satisfactory combination. Others are low-dose heparin and compression stockings (12), and low-dose heparin and dihydroergotamine (13-14).

Several stages in the pathogenesis of thrombosis are counteracted by the two media used in this study. Dextran causes

haemodilution and, by modifying factor VIII R:Ag, it diminishes platelet reactivity and enhances fibrinolysis (reviewed by Bergqvist (15)). Properly fitted graded compression stockings with the highest pressure distally increase the venous flow rate (16-17) and clear stagnant blood from the venous cusps (18). The Tubigrip^R type of stocking with a cylindrical shape has not been found to counteract thrombosis, (19-20) and it does not increase the flow rate (16).

The compression pressure achieved by graded stockings is not so great that plasminogen activators are released from the vein wall (21).

An increase in vein flow rate can also be obtained pharmacologically by increasing the venous tonus with dihydroergotamine, and it has recently been shown that dihydroergotamine enhances the thromboprophylactic effect of dextran 70 in hip fracture patients, (22) thus making it another possible alternative.

As measured by the ¹²⁵I-fibrinogen test, and compared with controls and heparin, dextran only provides an intermediate reduction in the frequency of postoperative thrombosis (1). Therefore the further reduction obtained by using graded static compression is of practical significance.

The overall frequency of thrombosis in this study is somewhat lower than what has been found with only dextran prophylaxis among similar patients earlier (23-24), and decidedly lower than among untreated patients (23, 25). Spiro et al (26) showed an increase in contralateral femoral vein flow when applying splints of different pressures to one leg and theoretically the use of one control leg and one leg with stocking in the same patient may be open to criticism. In their experiments, however, a kind of intermittent compression was used, and it is not known whether a static graded compression has a similar effect on the contralateral leg. This possibility, however, in no way affects our conclusions, since the reduced incidence of thrombosis in stockinged legs is beyond doubt.

With the introduction of dextran hapten inhibition, the frequency of anaphylactic dextran reactions can be substantially reduced (8-9), and prophylaxis with dextran and combinations with dextran are therefore also safe alternatives. Concern about side effects and complexity of administration are important factors when it comes to deciding which prophylaxis to use. As long as there is no simple method of recognizing risk patients pre-operatively (where development of postoperative thromboembolic complications is highly probable), prophylactic methods must be simple to attain general acceptance; four bottles of dextran 70 and graded compression stockings for one week is obviously one such alternative.

ACKNOWLEDGEMENT

The skilful technical assistance of Mrs Inger Olsson and Christina Cederlund has been greatly appreciated. This work has been supported by grants from the Swedish Medical Research Council (No. 00759), from Beiersdorf AB, Kungsbacka, Sweden, and from Pharmacia AB, Uppsala, Sweden.

REFERENCES

1. Bergentz S-E. Dextran in the prophylaxis of pulmonary embolism. *World J Surg* 1978;2:19-25.
2. Kline A, Hughes LE, Campbell H, Williams A, Zlosnick J, Leach KG. Dextran 70 in prophylaxis of thromboembolic disease after surgery; a clinically oriented randomized double-blind trial. *Br Med J* 1975;2:109-112.
3. Gruber UF, Saldeen T, Brokop T, Eklöf B, et al. Incidences of fatal postoperative pulmonary embolism with dextran 70 and low-dose heparin. An International Multicenter Study. *Br Med J* 1980;280:69-72.
4. Gruber UF. Prevention of fatal postoperative pulmonary embolism by heparin dihydroergotamine or dextran 70. *Br J Surg* 1982;69:554-558.
5. Allan A, Williams JT, Bolton JP, Le Quesne LP. The use of graduated compression stockings in the prevention of postoperative deep vein thrombosis. *Br J Surg* 1983;70:172-174.
6. Holford CP. Graded compression for preventing deep venous thrombosis. *Br Med J* 1976;2:969-970.
7. Scurr JH, Ibrahim SZ, Faber RG, Le Quesne LP. The efficacy of graduated compression stockings in the prevention of deep vein thrombosis. *Br J Surg* 1977;64:371-373.
8. Ljungström K-G, Renck H, Hedin H, Richter W, Rosberg B. Prevention of dextran-induced anaphylactic reactions by hapten inhibition. I. A Scandinavian multicenter study on the effects of 10 ml dextran 1, 15 %, administered before dextran 70 or dextran 40. *Acta Chir Scand* (In Press).
9. Renck H, Ljungström K-G, Hedin H, Richter W. Prevention of dextran-induced anaphylactic reactions by hapten inhibition. III. A Scandinavian multicenter study on the effects of 20 ml dextran 1, 15 %, administered before dextran 70 or dextran 40. *Acta Chir Scand* (In press).
10. Kakkar VV, Howe CT, Flanc C, Clark MB. Natural history of postoperative deep-vein thrombosis. *Lancet* 1969;2:230-232.
11. Bergqvist E, Bergqvist D, Bronge A, Dahlgren S, Hallböök T. Diagnosis of venous thrombosis in the lower limbs. A comparative study between ¹²⁵I-fibrinogen test, strain gauge plethysmography and phlebography. *Ups J Med Sci* 1973;78:191-199.
12. Törngren S. Low dose heparin and compression stockings in the prevention of postoperative deep venous thrombosis. *Br J Surg* 1980;67:482-484.
13. Bergqvist D, Efsing HO, Hallböök T, Lindblad B. Prevention of postoperative thromboembolic complications. A prospective comparison between dextran 70, dihydroergotamine heparin and a sulfated polysaccharide. *Acta Chir Scand* 1980;146:559-568.
14. Sagar S, Stamatakis JD, Higgins AF, et al. Efficacy of low-dose heparin in prevention of extensive deep-vein thrombosis in patients undergoing total hip replacement. *Lancet* 1976;1:1151-1154.
15. Bergqvist D. Dextran and haemostasis. A review. *Acta Chir Scand* 1982;148:633-640.
16. Arnoldi C. Elastic compression in the prevention of venous thrombosis. *VASA* 1976;5:101-106.

17. Sigel B, Edelstein A, Savitch L, Hasty J, Felix R. Type of compression for reducing venous stasis. A study of lower extremities during inactive recumbency. *Arch Surg* 1975;110:171-175.
18. Lewis C, Antoine J, Mueller C, Talbot W, Swaroop R, Edwards S. Elastic compression in the prevention of venous stasis. A critical reevaluation. *Am J Surg* 1976;132:739-743.
19. Browse NL, Jackson BT, Mayo ME, Negus D. The value of mechanical methods of preventing postoperative calf vein thrombosis. *Br J Surg* 1974;61:219-223.
20. Rosengarten D, Laird J, Jeyasingh K, Martin P. The failure of compression stockings (Tubigrip) to prevent deep venous thrombosis after operation. *Br J Surg* 1970;57:296-299.
21. Ljungnér H, Bergqvist D, Nilsson IM. Effect of intermittent pneumatic and graded static compression on factor VIII and the fibrinolytic system. *Acta Chir Scand* 1981;147:657-661.
22. Bergqvist D, Lindblad B, Ljungström, K-G, Persson N, Hallböök T. Does dihydroergotamine potentiate the thromboprophylactic effect of dextran 70? A controlled prospective study in general and hip surgery. *Br J Surg*, in press.
23. Bergqvist D, Hallböök T. Prophylaxis of postoperative venous thrombosis in a controlled trial comparing dextran 70 and low-dose heparin. A study with the ¹²⁵I-fibrinogen test. *World J Surg* 190;4:239-243.
24. Bergqvist D, Ljungnér H. A comparative study of dextran 70 and a sulphated polysaccharide in the prevention of postoperative thromboembolic complications. *Br J Surg* 1981;68:449-451.
25. Törngren S, Forsberg K. Concentrated or diluted heparin prophylaxis of postoperative deep venous thrombosis. *Acta Chir Scand* 1978;144:283-288.
26. Spiro M, Roberts VC, Richards JB. Effect of externally applied pressure on femoral vein blood flow. *Br Med J* 1970;1:719-723.

